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SOLUBILIZATION

H. B. KLEVENS¹

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I. INTRODUCTION

A considerable amount of literature has been devoted to the various phenomena associated with surface-active agents. The problems of hydrotropy, solubilization, emulsification, and blending have made up an appreciable fraction of these reports, but unfortunately by far the greater part of this work has been done with soaps and detergents which have not been well characterized, since they were essentially commercial preparations. That these data are important from the point of view of application is clearly accepted, but no information can be obtained from them as to the various factors which influence solubilization. During the past few years, attempts have been made in a few laboratories

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to distinguish between these factors and to determine various types and mechanisms of solubilization.

To restrict somewhat the scope of the term "solubilization," it is necessary to define the companion terms "hydrotropy," "blending," and "emulsification." Neuberg (178) used the term "hydrotropy" to designate the increase in solubility in water of various substances due to the presence of large amounts of additives. Thus the presence of 25–50 per cent of sodium benzoate, benzene-sulfonate, or others of this class increases the solubility in water of aniline, amyl alcohol, toluene, benzoic acid, and others. The solubility of benzoic acid is increased from 2.9 to 8.7 g. per 1000 g. when 2 N (about 50 per cent) sodium benzenesulfonate solution is used as the solvent in place of water (57). These phenomena must be due to a change in solvent, for essentially large proportions of this good solvent (additive) are necessary to bring about these increases in solubility. McKee (166) pictures this process as a salting-in effect in contrast to the well-known phenomenon of salting-out. However, it is necessary to understand that the classification of hydrotropy and solubilization as separate phenomena (144, 178) is not necessarily valid. There is a continuous gradation in the behavior of the sodium salts of fatty acids as solubilizers as the chain length increases (44a, 50, 178, 254). In ascending an homologous series, as from C₁ to C₁₁ normal fatty acid soaps, there is a gradual change in solubilizing (= hydrotropic) properties (44a), just as there is found a twofold decrease in critical micelle concentration with each addition of one carbon atom to the normal alkyl chain (82, 109). For the lower members of this series, the solubilizing properties become evident at high concentrations (30–50 per cent); for the higher members, this concentration is much lower, but the general character of the processes involved is characteristically the same throughout (254).

A similar type of salting-in phenomenon is observed in the increase in solubility of polycyclic hydrocarbons, such as benzanthracene, in solutions of purine and pyrimidine bases as compared with water as a solvent (249). This enhanced solubility, a type of hydrotropy, has been shown to involve complex formation between added solvent and solute molecule, as evidenced by a decrease in fluorescence of the polycyclic hydrocarbons (250). It is possible that the salting-in phenomena, observed in those cases where the added solvent molecule is structurally similar to that of the solute molecule, would also involve the formation of complexes. Another method which would indicate hydrotropy is the phenomenon involved in those cases where there are spectral changes observed with the use of different solvents. Thus, the spectrum of 1,2,5,6-dibenzanthracene is observed to change when *n*-heptane is replaced by benzene or by 1-methylnaphthalene as a solvent (120).

Blending (182, 184) is a broad term which has been distinguished from solubilization by recourse to phase diagrams (8, 184, 248). This process involves the blending or mutual solubility of two normally immiscible solvents by the addition of a colloidal electrolyte. Thus, dodecylamine hydrochloride added to chloroform even in low percentages enables the chloroform to dissolve large quantities of water, up to 45 moles of water per mole of detergent. Conversely,

the presence of water enables the chloroform to dissolve about one-fourth of its weight of dodecylamine hydrochloride, although both these substances are nearly insoluble in water (182).

Solubilization has been defined by McBain as the spontaneous passage of solute molecules of a substance insoluble in water into an aqueous solution of a soap or a detergent in which a thermodynamically stable solution is formed (144). The formation of such a system involves a decrease in free energy which indicates its thermodynamic stability. Solubilization involves the diffusion of the added solute molecules from bulk phase (insoluble solids, oil droplets, etc.) into the soap micelle. Beyond the point of saturation of the micelle with added solute, emulsification is seen to occur by the appearance of turbidity in those cases where the added solute is liquid in nature. Thus, the formation of a more or less stable system in which the dispersion of the added insoluble liquid is of such a nature that there is an appearance of turbidity due to the presence of the droplets of additive can be used as an indication of emulsification. It is then apparent that normally these two phenomena, solubilization and emulsification, can co-exist, the latter beginning when the former reaches its limit. Hartley (84) objects to the use of a new term, "solubilization," to define the conditions described above, in that it appears to imply that an essentially new process is under investigation and that it is often held that the resulting solutions are not in equilibrium. The peculiarity is that the solvent is unusual in structure rather than that the solute is brought into an unusual state. Thus, a much smaller amount of a paraffin-chain salt than of acetone is necessary to bring a long-chain alcohol and water into complete miscibility. However, since the solvent power of the colloidal electrolyte, in contrast to that of acetone, is fairly constant over a wide concentration range, it is felt by this reviewer that the use of an apparently new term is justified. The current wide acceptance of the term also may validate its use.

Winsor (254) has extended the point of view put forward earlier by Lindau (137) and by von Hahn (246) that hydrotropy and solubilization are essentially similar processes. Qualitatively, this is based on the fact that the attractive forces between molecules and ions in solution may arise from mutual satisfaction of *H* (hydrophilic) solvent affinities (A_H), e.g., solvent affinities dependent on hydrogen bonding, and *L* (lipophilic) solvent affinities (A_L), e.g., van der Waals forces. Between any two species *O* (oil) and *W* (water) in a single liquid phase, the total intermolecular solvent attraction can be represented qualitatively as:

$$A_{OW} = A_{HO_W} + A_{L_O W}$$

The attraction will depend in detail on solvent affinities and concentrations of both *O* and *W* (242). The point of view extended by Winsor is not in opposition to the micelle theories of solubilization (144) but is considered supplementary to them. He attempts to correlate phase changes,² which are the observed results of

² The problem of the use of the word "phase" in connection with soap solutions requires some clarification at the present time. Since it is agreed that soap solution and solubilized (dissolved) organic liquid form a thermodynamically stable solution, this must be a single phase, since a solution by definition is a single phase. If a system contains two phases, con-

changes in composition and temperature, in terms of displacements of an underlying micellar equilibrium. In this review the micellar aspects of solubilization will be favored, for most of the available experimental findings can be readily understood by means of this approach.

The evidence of molecular association, for example, as advanced by solvent effects on the spectra of polycyclic hydrocarbons (120) and the change in fluorescence of polycyclics in the presence of purine and pyrimidine bases (250), which can be considered to be hydrotropic phenomena, can be seen to involve a binding of one solute molecule with one or more added solvent molecules. Clar (22) has shown recently that ovalene in 1-methylnaphthalene has absorption bands at 4650, 4600; 4560, 4480, 4280, 4035, 3890; 3490 Å., and corresponding bands are observed in benzene at 4635, 4585; 4525, 4450, 4250; 3450 Å. The increase in solubility of benzoic acid in water containing added sodium benzoate over that in water alone probably also involves a type of molecular association which is similar to that involving polycyclic hydrocarbons. However, association in the former case almost certainly involves hydrogen bonding between the $-\text{COONa}$, $-\text{COOH}$, and water on the one hand (hydrophilic association) and the operation of van der Waals forces between the C_6H_5 groups on the other (lipophilic association), whereas only the latter forces can be considered to be operative in polycyclic association. In the solubilization of polar type compounds, these two types of association forces are operative, whereas when hydrocarbons are being dissolved in soap micelles, it is primarily the lipophilic forces which are involved. These interactions require relatively high concentrations of reactants, often of the order of 1 to 2 *N*. On the other hand, solubilization is found to occur at much lower concentrations, first being noted at that concentration where micelles begin to form. This is called the critical micelle concentration (C.M.C.) and is often as low as $10^{-3} \cdot 10^{-4} M$. It has been shown to depend on such factors as chain length and structure of the surface-active agent, the presence of additives such as electrolytes, long-chain alcohols, amines, amides, etc., as well as temperature and the nature of the solvent. The effect of these factors on solubilization and the relationship of these results to the C.M.C. will be discussed below.

II. METHODS OF OBSERVATION

There are a number of methods for determining the extent of solubilization which depend on the structure of the solubilizate (the substance being solubi-

tinuous and discontinuous, then by definition it can not be termed a solution. It must be recognized, however, that there are regions in these solutions in which there is practically nothing but paraffin-chain molecules (micelles) and other regions which contain water and simple ions. These latter systems approximate in their behavior to a two-phase system in certain respects, e.g., solvent power, but they are of course fundamentally different in others. It is convenient, though thermodynamically inaccurate, to classify certain of these systems as having a water-continuous phase or environment and others as having a hydrocarbon-continuous one. This concept must be considered to have only a geometrically descriptive meaning. The essential difference between the two-phase oil-water emulsion system and the "two-phase" soap solution is that the size of the region is of considerably different fundamental thermodynamic importance in the two cases. In a series of letters between Dr. G. S. Hartley, Dr. P. A. Winsor, and the author, it was deemed necessary that these concepts be clarified; the above discussion has made free use of this correspondence.

ized), the difference in refractive indices of soap solution and solubilizate, the vapor pressure of the solubilizate, and various other factors. Various methods which have been used and a few typical examples of each will be discussed.

A. OPACITY METHOD

If the refractive indices of the soap or detergent solution and the solubilizate (usually a liquid) are different, then the presence of solubilizate aggregates or droplets in the soap solution will be evidenced by a turbid appearance of the system. This onset of turbidity, due to the formation of aggregates, has been used to indicate the limit of solubilization. This phenomenon was utilized as early as 1892 by Engler and Dieckhoff (50) to determine the solubility of a series of hydrocarbons in various soap solutions and has since been used by many others.

To definite amounts of soap solutions in a series of vials, there are added known but different amounts of solubilizate. These vials are then shaken for from 1 to

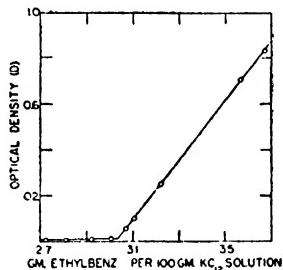


FIG. 1

FIG. 1. Limit of solubilization of ethylbenzene in 0.63 M potassium dodecanoate per 1000 g. soap solution as determined turbidometrically (25°C.).

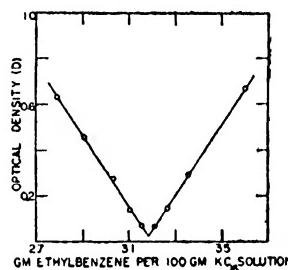


FIG. 2

FIG. 2. Solubilization of ethylbenzene in 0.21 M potassium hexadecanoate per 1000 g. soap solution (35°C.).

60 days, for it has been shown that equilibrium is only reached in from 24 to 60 hr. when hydrocarbons such as *n*-heptane, benzene, or ethylbenzene are being solubilized (86) and as many as 60 days are required when very insoluble polyacenes such as benzanthracene and dibenzanthracene are the solubilizates (113). Typical of the data obtained by these opacity measurements are the curves in figures 1-3.

If soap solutions are initially clear, transparent systems, then the addition of solubilizate will show opacity characteristics similar to those observed in figure 1. The initial potassium laurate (KC₁₂) solution has an optical density (D) of about zero. Addition of various amounts of a hydrocarbon such as *n*-heptane or ethylbenzene or a polar compound such as 1-heptanol or *n*-heptylamine will show little or no change in D until the point of maximum solubilization. Any more solubilizate added will result in the formation of oil droplets (emulsification), as can be seen by a marked increase in D. The intersection of these two lines is taken as the point of maximum solubilization.

In those cases where the initial soap solution is initially opaque, as when potassium stearate (KC_{18}) solutions are used as solubilizers, the addition of solubilizate will cause an initial decrease in D until a relatively transparent solution is obtained. An example of this type is seen in figure 2 and, as above, the point of maximum solubilization is the intersection of the two lines. The initial decrease in turbidity upon addition of solubilizate is due to a decrease in size of the aggregated micelles.

Recently (112) opacity curves similar to that in figure 3 have been obtained in those cases of solubilization of hydrocarbons by long-chain polar compound-soap micelles. If, for example, the amount of 1-heptanol added initially exceeds its normal solubility in KC_{14} solutions and if, to these solutions, are added various amounts of *n*-heptane or ethylbenzene, changes in turbidity following the

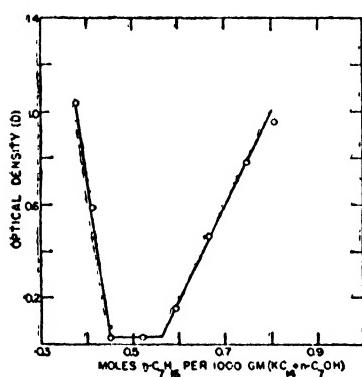


FIG. 3

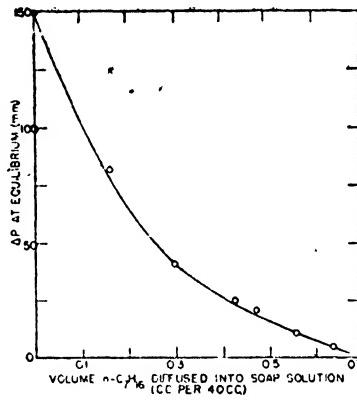


FIG. 4

Fig. 3. Solubilization of *n*-heptane in soap-alcohol micelles (0.375 M potassium tetradecanoate plus 0.315 M 1-heptanol) at 25°C .

Fig. 4. Difference in vapor pressure between *n*-hexane-water and soap solution during progressive addition of *n*-hexane to 5.62 g./100 ml. potassium oleate solution (159).

curves in figure 3 are obtained. The initial opacity is due to the presence of droplets of 1-heptanol emulsion in equilibrium with mixed KC_{14} -1-heptanol micelles. Addition of *n*-heptane, which enters the hydrocarbon-like center of the micelle, causes the micelle to swell, and, simultaneously, more alcohol molecules pass from the emulsion droplets through the water to the alcohol-soap micelle. This is indicated by the initial decrease in opacity. As more *n*-heptane is added, the micelle swells more until all emulsified alcohol has been solubilized. Addition of further *n*-heptane to this clear system yields the typical two straight lines as in figure 1, in which the intercept is the limit of solubility. This limit is then the second transition point. These results will be discussed below in the light of the various loci of solubilization which are present in the soap micelle.

It can be seen that the opacity method is readily applicable to systems in which the solubilizate is a liquid, for in these examples the initial formation of liquid droplets of solubilizate can be used as an indication of the extent of

solubilization. Davis, Krahl, and Clowes (31) measured the solubility of polycyclic hydrocarbons in water by a turbidometric method. They used concentrated solutions of the polycyclics in acetone or ether and added weighed amounts of these solutions to relatively large volumes of water. The acetone or ether was then boiled off under high vacuum and the turbidity of the system was measured by a sensitive Tyndallometer. It was assumed by these authors that the dissolved polycyclics were molecularly dispersed and that the limit of solubility involved the precipitation of microcrystals of these hydrocarbons. The solubilities of polycyclic hydrocarbons in water obtained by the turbidity method were essentially in agreement with those obtained by spectroscopic measurements, in which advantage was taken of the presence of absorbing chromophores in these compounds (113). There is no literature on the application of this technique to the solubilization of solids, but experiments using this method are now in progress in this laboratory to determine the solubilization of long-chain hydrocarbons such as *n*-octadecane, *n*-eicosane, and *n*-docosane. The preliminary results indicate that this method may be applicable for the determination of solubilities in soap solutions of those solid compounds which do not have absorbing chromophores or other properties which can be used as indications of saturation.

B. SPECTRAL METHOD

The presence of absorbing chromophores in solubilizates can be readily used to determine the degree of solubilization, especially in the cases where the compound being studied is a solid. Essentially, to soap solutions of known concentration, crystals of solubilizate are added and the system is shaken until equilibrium is reached. In those cases of solubilization of dyes such as Orange OT (*o*-tolylazo- β -naphthol) and Yellow AB (phenylazo- β -naphthylamine), McBain and collaborators (144, 155, 163) have found that equilibrium conditions were only reached after days and even weeks. Solubilization equilibrium of very slightly soluble polycyclics such as 1,2,5,6-dibenzanthracene was only reached after almost two months (113) at room temperature. Lambert and Busse recommend the use of 50°C. for the solubilization temperature instead of 25°C. and report that solubilization values sufficiently close to the equilibrium values could be obtained within 15 min. if the tests were made at 50°C. and if the amount of dye to be solubilized does not exceed certain limits (131). This latter method might be suitable for the comparison of results using various dyes and solubilizer systems but might not find general application. Kolthoff and Stricks (125) found that there was an increase in the solubilization of dimethylaminoazobenzene in various detergents when the temperature was increased from 30°C. to 50°C.

After equilibrium is reached, aliquots are removed from the solubilization system and diluted by suitable solvents. Care should be taken that no solid solubilizate is included with the aliquot. The spectral characteristics of the solubilizate which had been determined previously are used as a standard and by means of the proper use of the Beer-Lambert law, it is possible to calculate the concentration of the compound which has been solubilized. The spectra of colored com-

pounds can, of course, be measured in the visible region, whereas use must be made of the ultraviolet region for compounds such as the polycyclic hydrocarbons. Solid residue, nonsolubilized solubilizate, may be allowed to settle for a number of days before removing aliquots or recourse to centrifugation may be made to hasten this process. Extreme care must be taken to insure that there is no suspending and protecting of these solid solubilizates in addition to solubilization. In the experiments of McBain and Woo (164), it was indicated that, in addition to solubilizing the dye (Yellow AB), there was also considerable suspending and protecting of colloidal particles of the dye, which resulted in too large values of solubilization.

C. VAPOR PRESSURE METHOD

Since there is a decrease in the vapor pressure of an insoluble volatile liquid when the medium is changed from water to a soap solution, McBain and O'Connor (158) were able to measure the solubilization of various volatile organic compounds. The colloidal solutions formed when volatile organic liquids are allowed to come in contact with soap solutions are thermodynamically stable because the vapor pressure is significantly less than that of the free hydrocarbon until the solution is approximately saturated.

Typical of the type of experimental results obtained by these measurements are the curves in figure 4 (158). Equilibrium vapor-pressure values are plotted and indicate the increase in vapor pressure of the indifferent hydrocarbon as the soap solution gradually becomes saturated with solubilized hydrocarbon. Saturation is reached when the vapor pressure of the hydrocarbon over the soap solution reaches its value over water. This method is not very sensitive to changes in environment, for the addition of various electrolytes does not show effects corresponding to those observed by other methods (159).

D. OTHER METHODS

X-ray measurements have indicated an increase in spacing of a particular band upon addition of hydrocarbon. (The interpretation and discussion of these patterns as related to micellar structure will be advanced later.) Thus, Kiessig and Philippoff (101) have indicated that the long x-ray spacings of a 9.12 weight per cent sodium oleate solution increase from 91 Å. to 127 Å. upon the addition of 0.791 g. of benzene per gram of oleate. There is a gradual increase in spacing upon increment addition of hydrocarbon until the saturation point is reached. Beyond this point, further addition of hydrocarbon will result in little or no increase in this x-ray spacing. Thus, Mattoon (73) has shown that in the solubilization of *n*-heptane in 25 per cent potassium laurate (KC_{12}) the value of ΔD_I (x-ray increment of intermicellar spacing in Ångström units) varies according to the relation:

$$\Delta D_I = 3.82C$$

where C is grams of *n*-heptane per 100 g. of soap plus water. Above a C -value of 3.6, the ΔD_I -values are constant. Thus, the measure of change in long x-ray

spacing could be applied to the determination of solubilization and the limit of solubilization could be obtained at that concentration of C when ΔD_I began to be constant. Similarly, McBain and Hoffman (150) have shown from x-ray measurements of 50 per cent KC_{12} solutions that there is a linear increase in ΔD_I with added cumene up to a saturation limit where ΔD_I remains constant with further addition of oil. Up to the constant value the systems are clear; at oil concentrations above this, they appear cloudy.

There are indications from x-ray measurements that the molecular weights of soap micelles increase with added hydrocarbon. (The added hydrocarbon is not included in these calculations.) Preliminary light-scattering measurements at concentrations of added hydrocarbon just below saturation indicate about a doubling of the number of soap molecules per swollen micelle as compared with the hydrocarbon-free micelle (113). This latter method could be modified so as to determine the amount of hydrocarbon solubilized at a point just under saturation. Above this saturation value, the presence of oil droplets would interfere considerably.

In summary of the available methods, it can be seen that for liquid solubilizes whose refractive indices are not the same as that of the soap solution the turbidometric method would be simplest. For solids with absorbing chromophores in either the visible or the ultraviolet, the spectral method can be readily applied. For vapors, the vapor pressure method is applicable, and for indifferent solids such as solid alkanes or solid olefinic compounds (nonconjugated systems), a modification of the method of Davis *et al.* (31) could be used.

Since the absorption of a simple monoolefin has a maximum at about 1860 Å. (189) with a shift to about 1960 Å. with further alkylation (188), the measurement of solubilization of compounds of this class by spectral means would require the use of a fluorite vacuum spectrograph of the Cario-Schmitt-Ott type. However, it has been shown that many of these compounds have long-wave-length absorption tails which extend into the quartz region to about 2050-2100 Å. (119), and it has been possible to measure the solubilization of a number of biologically important sterols such as cholesterol and isocholesterol in this manner (118).

The presence of minima in surface tension and interfacial tension measurements has been attributed to the presence of impurities (173, 219, 221) which may be removed by foam extraction or by solvent extraction. This might be considered to be applicable as a method of determination of solubilization in the region of the critical micelle concentration for, although the minima occur at about the same surface tension values (221), the shapes of the surface tension-concentration curves with different amounts of additive are sufficiently different to warrant their use as indicators of solubilization.

III. TYPES AND MECHANISMS OF SOLUBILIZATION

The possibility of hydrotropy as one of the types of solubilization can be ruled out on the basis of the mechanisms involved. The phenomenon of hydrotropy involves the use of very large amounts, as much as 2 N or more, of the additive

and probably acts through the processes of molecular association. This can be considered to be a solvent effect similar to that which has been observed in solvent effects with polycyclic hydrocarbons (22, 120-249, 250) (however, *vide supra*).

A number of other possibilities present themselves. First is the possibility of adsorption on the surface of the micelle; second, incorporation in the hydrocarbon center of the micelle, a form of solution; and third, incorporation by penetration into the palisade layer of the micelle with the solubilizate oriented in approximately the same manner as is the soap molecule in the micelle. These three possibilities will be discussed in detail below.

A. ADSORPTION BY THE MICELLE

The formation of films at liquid-liquid or at liquid-solid interfaces is such a common phenomenon that it is to be expected that solubilization would involve, to some degree, this action at the soap micelle-water interface. Whether this actually occurs is somewhat doubtful, as can be seen from the discussion below, but since definite evidence as to the absence of adsorption is not available, there is the possibility that this may play some role in solubilization.

When a charged dye such as pinacyanol chloride is added to a soap solution at concentrations below the C.M.C. there is often observed the formation of a precipitate (107), since the dye and the soap are oppositely charged. This insoluble complex salt is solubilized as the C.M.C. is passed by the addition of more soap to the system. As the C.M.C. is passed, there is a change in the association of the dye molecule which has been used as a method of determination of the C.M.C. (28). This would indicate that below the C.M.C. the dye molecules are in their P-form (dimer or higher) with one or more bound soap molecules, and that, upon solubilization, above the C.M.C. the dye goes to its M-form (monomer) when the soap molecules associate to form micelles. It must be accepted that the soap molecules which are acting as solubilizers and those of the soap-dye aggregates which are solubilized play an equal part in micelle formation and occupy essentially the same relative positions in the micelle. The charged, bound dye molecule, with a charge opposite to that of the soap molecules, thus can be considered to be adsorbed on the surface of the soap micelle, but it would appear more reasonable to expect that, because of their nonpolar nature, they would be more attracted toward the less polar region in the palisade layer of the micelle than toward the polar region of the water layer surrounding the micelle. It is probable that, since this dye is amphipathic, the charged end of the dye molecule penetrates into the water layer as does the soap molecule and the hydrocarbon end is oriented similarly to the corresponding hydrocarbon tail of the soap molecule. The penetration must be for only a very short distance, for the presence of the dye molecule does not decrease the C.M.C. by more than a few per cent. Also, the presence of short-chain soaps tends to increase the C.M.C. (105) and decrease the solubilizing power of longer chain soaps (114, 117). In contrast to these findings, the presence of short-chain alcohols (C_4-C_7) as additives decreases the C.M.C. (26, 199) and increases

markedly the solubilizing power for hydrocarbons (114). The effect of these additives on solubilization will be discussed in detail below, but they appear to indicate that if sorption by micelles occurs, it is probably the type which involves the least amount of penetration into the palisade layer of the micelle and does not necessarily mean that the sorbed molecule is sticking out from the micelle surface into the surrounding water layer. Thus, rather than classify this as a separate type of solubilization, it would appear that this should be, at most, a subclass of the incorporation by penetration group. McBain and McHan (154) have recently shown that there is a marked increase in the solubility of dimethyl phthalate in soap solutions over that in water. They postulate an adsorption on the micelle surface based on the fact that there is a decrease in the long x-ray spacing (150). It is more probable that these small polar compounds are not adsorbed on the micelle but rather penetrate only a very short distance into the palisade layer of the micelle. This is in accordance with the penetration of alcohols into the soap palisade layers, as shown by recent x-ray evidence (74), and with the marked enhancement of solubilization of hydrocarbons when alcohols are used as additives (112, 114). These points will be discussed in more detail in the following sections.

B. INCORPORATION INTO THE HYDROCARBON CENTER OF THE MICELLE

There is very direct evidence that the addition of hydrocarbons to soap solution involves penetration of these additives into the hydrocarbon center of the micelle. The extensive x-ray work of Krishnamurti (127), Hess and others (88, 101, 228), Hughes, Sawyer, and Vinograd (97), and Mattoon (73, 143) indicates that, from the increase in long x-ray spacings upon the addition of hydrocarbons, the solubilizate enters the hydrocarbon center of the micelle. These long x-ray spacings are supposed to correspond to the layers of soap molecules placed end to end and to a double layer of these soap "bundles" plus a portion of the water layer between this double layer and adjacent "bundles." It has been shown that with increase in soap concentration there was a corresponding decrease in this long x-ray spacing (101). Calculations from x-ray measurements as to the degree of expansion of the soap micelles with increase in concentration of added hydrocarbons assume that there is no change in the thickness of the water layer during solubilization. On the basis of this extensive x-ray work, it has been proposed that solubilization takes place in these adjacent "bundles" or lamellar micelles (73, 144). Typical of the manner in which these findings are represented are the diagrams in figure 5, in which highly idealized schematic diagrams of both the lamellar micelle of McBain (144) and the spherical micelle of Hartley (79), with and without added hydrocarbon, are shown.

The expansion of the long x-ray spacing, D_L , which is associated with the distance between adjacent double layers of soap molecules and which varies with soap concentration, has been the foremost argument advanced for the existence of the lamellar micelle (144). However, it should be noted that these same x-ray data can also be interpreted in the light of the manner in which the two-layer micelles (spherical or oblate spheroid) pack. This concept has been

advanced by Hartley (81) and will be discussed below in the section on structure and organization in soap solutions (Section IX). Recently, it has been shown that there is another very weak x-ray band, the spacing, D_M , which appears to be that of the double-layer micelle (143). This x-ray spacing is found to be independent of concentration, a fact which supports its identification as the two-layer micelle band. The D_M spacing has been shown to increase with added hydrocarbon, reaching a maximum at the limit of solubilization.

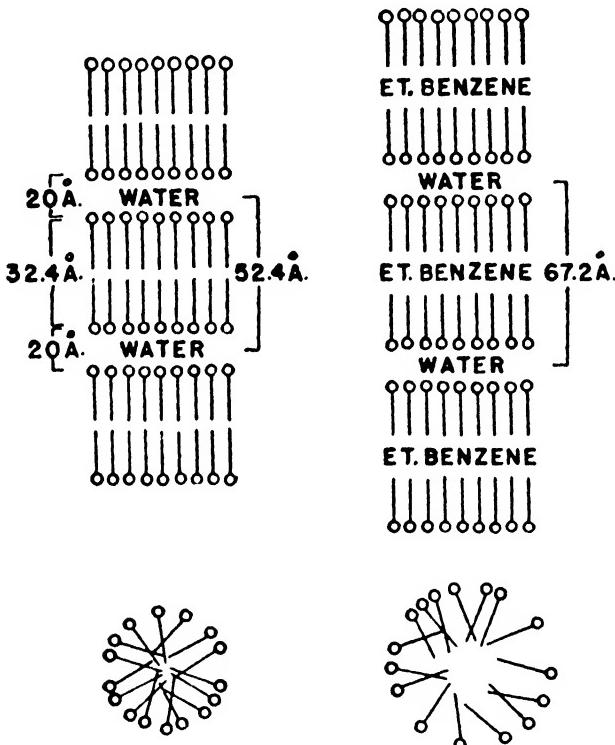


FIG. 5. Highly idealized schematic diagram of 0.63 N potassium laurate solutions showing effect of added ethylbenzene. Lamellar micelle of McBain and spherical micelle as pictured by Hartley are shown.

It was found that the solubility of azobenzene in aqueous solutions of cetyl-pyridinium chloride is approximately the same as in an equivalent amount of hexadecane (80), indicating that there is essentially a liquid paraffinic interior in the soap micelles. This will hold, of course, only for nonpolar solutes and will not be at all applicable to polar solubilizates which have a different locus of solubilization in the soap micelle.

Typical of the solubilization data is the solubilization of *n*-heptane in potassium tetradecanoate, shown in figure 6. In the solubilization of all simple hydrocarbon compounds, e.g., the liquid paraffins, benzene and alkylated benzenes,

etc., it is noted that the rate of solubilization increases with increasing soap concentration. As the size of the hydrocarbon increases, as when the solubilizates are polycyclic hydrocarbons, the rate becomes constant (113). When simple polar compounds such as dimethyl phthalate (154), long-chain alcohols and amines up to about C_{10} (75, 112) are solubilized, the rate of solubilization decreases with increasing soap concentration. The data for 1-heptanol in KC_{14} are included in figure 6 for comparison. When the size of the polar compound increases, as when polar dyes, alcohols of C_{10} or more, etc. are the solubilizates, this rate again becomes fairly constant. It is evident that there are transition compounds which behave somewhat like the hydrocarbons in solubilization because the nonpolar portion of the molecule is large enough to counterbalance any influence exerted by the polar group.

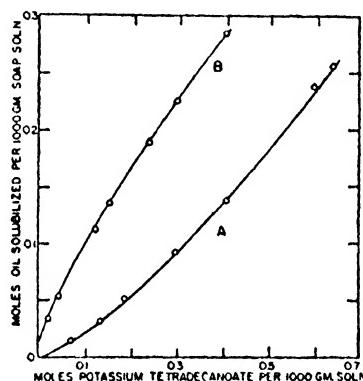


FIG. 6. Solubilization of *n*-heptane (A) and 1-heptanol (B) in potassium tetradecanoate solutions (25°C.).

It has been suggested (111, 254, 255a) that in any discussion of solubilization and solubilizing power (moles of oil solubilized per mole of micellar soap) it is necessary to distinguish between two quite different limiting cases of solubilization. In one type, as is exemplified by the solubilization of *n*-heptane, the limit is reached when the hydrophobic micellar regions can dissolve no more heptane and excess hydrocarbon separates as a phase containing negligible amounts of the other components of the system. In the other type, as in the solubilization of 1-heptanol, the limit is approached when the micellar regions of the solution become sufficiently lipophilic on account of the inclusion of the long-chain alcohols in the soap layer (penetration into the palisade layer of the micelle) to cause the separation of two phases. The fact that there are observable marked differences in viscosities of these alcohol-swollen and hydrocarbon-swollen micelles and that the micellar weights of the alcohol-soap micelles are at least ten times as large as those of the hydrocarbon-soap micelles (118, 121a) indicates that the limiting micellar structure causing phase separation in the first type is probably quite different from that causing separation in the second. Winsor (255a) further suggests that these micellar structures are limiting forms of

S_1 (hydrophilic layer on the surface of some form of "globular" micelle) and S_2 (hydrophilic layer predominantly towards the inner portion of a "globular" or lamellar micelle) types of micelles, respectively.

C. PENETRATION INTO THE PALISADE LAYER OF THE MICELLE

Solubilization of polar compounds such as alcohols, amines, longer chain soaps, fatty acids, insoluble soaps, various polar type dyes, possibly some mercaptans, etc. can be considered to involve penetration into the palisade layer of the soap micelle rather than incorporation into the micelle center. Solubilization of this type involves a more or less oriented solubilizate with reference to the position of the soap molecule in the micelle. Schulman and Hughes (211) have shown that mixed films of alcohol and soap are possible, as was indicated by an increase in film pressure when a solution of sodium hexadecyl sulfate was injected under a condensed monolayer of hexadecyl alcohol. This type of evidence, coupled with characteristic x-ray studies in which it has been indicated that there is no increase, but at times a decrease, in x-ray spacing, D_M , and also with typical solubilization data of polar compounds, supports the concept that solubilization takes place in the palisade layer of the soap micelle.

Probably the first indication of polar type solubilization in which there was no increase in long x-ray spacing was that involving the changes in D_I spacing for soap mixtures (72). Unrecognized by these authors was the fact that, since the long spacing of mixtures of KC_{12} and KC_{14} is a linear function of the mole ratio of the two soaps, solubilization of the less soluble soap by the other must involve penetration into the palisade layer. If there were any other type of solubilization involved, the long x-ray spacing would have to go through a maximum. More recent x-ray evidence on the changes in D_I with added dimethyl phthalate indicates a decrease with concentration of solubilizate (150). This same D_I spacing is seen to decrease with added alcohol, reaching a minimum for the C_3 alcohol, and to increase above that of the water value for C_6 and longer alcohols (74). However, when the micellar band, D_M , is considered, all spacings decrease below the alcohol-free value for alcohols up to C_{10} when the solubilizer is sodium dodecyl sulfate. It is quite likely that for the longer chain alcohols— C_{12} , for example— ΔD_M would be approximately zero. No data have been reported for this solubilizate, probably because of the experimental difficulties involved in the preparation of these systems. 1-Dodecanol, with a melting point of about 22–23°C., is found to solidify upon addition to soap solutions at room temperature and requires heating to disperse it completely (115). 1-Dodecanol, as well as other added long-chain polar compounds, and soap solution readily produce a viscous birefringent gel (115, 254) and this gel formation is especially marked in systems containing 1-alkanols in conjunction with 1-alkane salts (254, 255). Transition effects have been noted in comparing the solubilization of hydrocarbons and of long-chain alcohols in soap-electrolyte solutions (115). Thus, 1-decanol and 1-dodecanol appear to have solubilization properties intermediate between those of the shorter chain alcohols, up to C_8 , and those of *n*-heptane in KC_{14} -potassium chloride solutions. When a shorter chain soap is

used, as when KC_{12} -potassium chloride is the solubilizer, 1-octanol is seen to behave like a transition solubilizate between the shorter chain alcohols and hydrocarbons such as *n*-heptane (118).

Typical of this class of solubilizate, exhibiting properties which are interpreted as leading to solubilization in the palisade region of the two-layer soap micelle, is the example of 1-heptanol in KC_{14} included in figure 6. As mentioned above, in comparison with hydrocarbons, the rate of solubilization of this polar compound is seen to decrease with increase in soap concentration. A relatively unrecognized case of this type of solubilization (111) is the increase in solubility of insoluble calcium dodecylsulfonate in solutions of their corresponding sodium salts (233). Soap mixtures such as potassium laurate and potassium palmitate should be also included in this group (220), for the less soluble palmitate could be considered to be solubilized by the laurate (111). Similar types of solubilization data have been obtained in mixtures of lithium and potassium laurates (118).

The solubilization of various polar dyes, such as Orange OT (1-*o*-tolylazo-2-naphthoi) in potassium laurate solutions (149) and Yellow AB (phenylazo- β -naphthylamine) in aqueous sodium desoxycholate and in laurylsulfonic acid solutions, has been thoroughly investigated by McBain and coworkers (157) and these data show properties characteristic of penetration of these molecules into the palisade layer of the soap micelles rather than solubilization in the hydrocarbon center of the micelle.

The solubilization of *n*-heptane in KC_{14} illustrated in figure 6 and many other similar data on a large number of polar and nonpolar solubilizates indicate that solubilization begins at the C.M.C. Below this concentration, it is assumed that no micelles are present and various experimental measurements such as conductivity, transference number, freezing-point depression, etc. show that the colloidal electrolytes at these concentrations are nonassociated. Below the C.M.C. the soap acts like an electrolyte, causing a decrease in the solubility of the hydrocarbon or the polar compound, such as another soap, below that in water owing to the well-known salting-out effect. This has been shown to occur in the case of ethylbenzene in KC_{12} (86) and in the decrease in solubility of calcium dodecylsulfonate in solutions of sodium dodecylsulfonate below the C.M.C. of the latter soap (233). It might be supposed that solubilization begins below the C.M.C., as observed in the appearance of color in insoluble dye-soap (below the C.M.C.) mixtures (125). However, the amounts dissolved are so small—often only a few per cent more than is soluble in water—that the individual dye molecule must be considered to be bound, at first, either by electrostatic or van der Waals forces, with an individual soap molecule. The fact that solubilization begins at the C.M.C. has been utilized in the determination of the C.M.C. (125, 126). These C.M.C values determined by dye solubilization have been found to be in good agreement with those obtained by refraction (106, 107, 109), by changes in the spectral character of various charged dyes (28, 105, 107), by conductivity (202, 256), by solubility (235), and by various other methods.

Another method of plotting these data does not show the onset of solubilization at the C.M.C. as clearly as the method in figure 6 but it does give other

information. A plot of this type is shown in figure 7, where the manner in which the mole ratio (MR), moles of oil solubilized per mole of soap, varies with soap concentration is indicated. The curves in figure 7 for ethylbenzene (86) and Orange OT (149) indicate that the colloidal properties of potassium laurate begin just above the C.M.C., 0.025 M, and that this soap in the presence of hydrocarbons reaches full colloidal form at about 0.15 M. It is probable that, in the region between the C.M.C. and 0.15 M where the change in MR per unit soap concentration is greatest, both the size and the number of solubilizing soap aggregates, probably double-layer micelles, increase most rapidly. Above the concentration where the soap reaches its full colloidal form, there is probably only a small increase in micellar size. According to osmotic (146, 147) and conductance (153) measurements, this soap reaches full colloidal form in about

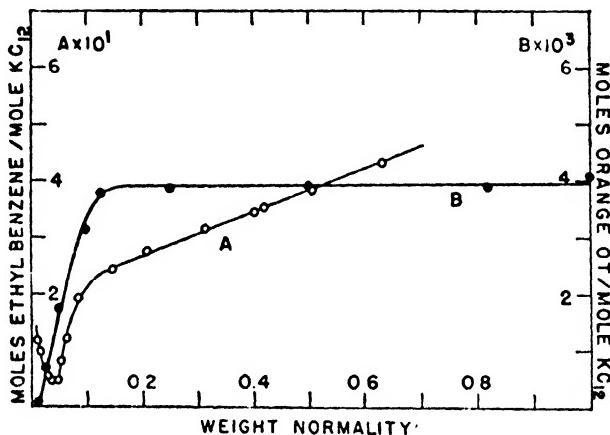


FIG. 7. Solubilization of ethylbenzene (A) and Orange OT (B) in potassium dodecanoate solutions (25°C.).

0.2 M aqueous solutions, a result which is in agreement with the concentration deduced from solubilization data.

IV. CHANGE IN CONTINUOUS MEDIUM

The major portion of the systems in which some substance other than water is the continuous medium involves the use of nonpolar hydrocarbons. The addition of soaps and detergents to various hydrocarbon systems will often result in a depression of the surface tension which might be associated with micelle formation. Thus the addition of about 0.1 per cent dodecylsulfonic acid to Nujol or mineral oil will result in decreases in surface tension of from 34 to 25 and 27.5 dynes/cm. (160). That phenomena similar to solubilization (= hydro-tropy) occur in these systems is indicated by the fact that the addition of as little as 0.2 per cent of dodecylsulfonic acid to an organic medium will result in an uptake of dye, as is seen by the system becoming colored; 15–20 per cent ethanol and 4–8 per cent glacial acetic acid added to toluene is necessary before

coloration is seen (156). The dyes used by these authors were eosin, fluorescein, crystal violet, and Calcomine Orange 2R (sodium *p*-sulfo-*o*-tolueneazo- β -naphthol) and use was made of both anionic and cationic detergents. No indication could be found from their data as to a preferential solubilization of a dye of one charge by detergent molecules of another charge.

Earlier Weichherz (244) had observed the uptake of water by solutions of soap in organic solvents. He found that ternary systems such as 79.94 per cent xylene, 12.91 per cent phenol, and 7.15 per cent sodium oleate remained homogeneous after the addition of 4.66 per cent water. It should be noted that this soap in xylene did not take up water. Pink (187) has shown that there is a linear relationship between water uptake and ethanolamine oleate concentration in benzene. Saturation was noted by the precipitation of the soap in a white curdy form. The addition of a large excess of water results in an inversion. In systems of aluminum palmitate in toluene, containing emulsified water, it was noted

TABLE 1
Solubilization of water in organic solvents by detergents at 20°C. (89)

DETERGENT	SOLVENT	WEIGHT OF WATER WEIGHT OF SOAP
Hexanolamine oleate . . .	Cyclohexane	1.35
	Benzene	1.34
	Carbon tetrachloride	0.99
	Chloroform	0.00
Laurylsulfonic acid	Chloroform	0.19
	Benzene	0.14
Cetylpyridinium chloride . . .	Nitrobenzene	0.00
	Chloroform	2.04

that, on cooling to -17.8°C ., 26 per cent of the water was found to be "bound" (102). It would appear from these measurements that this fraction of water, in the light of our present knowledge of solubilization, was solubilized water which probably was "bound" by hydrogen bonding to the polar groups in the interior of the inverted micelle.

From osmotic pressure measurements on aluminum dilaurate-benzene systems, it was postulated that this soap is an association colloid in benzene (165). A more complete investigation of these systems led to a number-average molecular weight as determined by osmotic pressure measurements of this colloid of about 500,000 when the concentration of aluminum dilaurate was 0.3 per cent in benzene (222). Solubilization of water in organic solvents containing added detergents has been measured by the turbidometric method and was also found to be slow in reaching equilibrium (185).

The data in table 1 indicate the effect of changes in structure of the solubilizer as well as changes in the solvent on the solubilization of water at 20°C . (185). The nonsolubilization of water in the chloroform-hexanolamine oleate system

is taken to be due to a competition and blocking of the carboxyl group by the solvent molecules. Cation-active soaps can supply the hydrogen bonding to the oxygen of the water molecules, and thus dodecylamine hydrochloride and cetylpyridinium chloride can solubilize water in the presence of chloroform. Bonding by nitrobenzene is sufficient to prevent water uptake by means of this mechanism.

Lawrence (133) has shown that soaps dispersed in oil are readily peptized by the addition of small amounts of polar compounds just as they are in aqueous systems and by the same sort of substances for the most part. It is seen that added water acts like other peptizers and that hydrolysis occurs (134). In conjunction with these systems, this author distinguishes between peptization and solubilization. The former term is used in its normal sense, meaning to increase the dispersion. Solubilization is considered to include three distinct cases: true internal solubilization of substances insoluble in water; solubilization of substances insoluble in water but containing polar groups, e.g., long-chain alcohols and amines, dyes; and those cases where the soap is peptized by the substance solubilized. This author speculates on the various complexities involved in soap and oil systems and emphasizes the importance of the presence of impurities in relation to various reported data.

Up to the present time there have been no very extensive measurements on the solubilization of polar compounds in soap-hydrocarbon systems. Based on previous findings that micelle formation in aqueous systems in the presence of certain dyes (28, 107) results in spectral changes in these dyes, it has been found that rhodamine B will fluoresce in soap-hydrocarbon systems above a certain soap concentration (6). Since the fluorescence increases with increasing concentration of soap (indicative of dye dissociation), it is evident that there is an increase in micellar size with concentration in these systems. By the use of this dye, calcium xylylstearate and calcium xenylstearate were shown to have C.M.C. values of 1×10^{-6} mole/liter and 8×10^{-6} moles/liter, respectively. The anhydrous calcium xenylstearate (3.48 g. of soap per 100 ml. of benzene) is found to be extremely viscous and the addition of as little as 0.05 per cent of water will convert this system to a mobile liquid (7). This is assumed to involve a breakdown of thread-like aggregates, termed micelles (probably incorrectly) by these authors.

Schulman and Riley (215) studied the change in x-ray patterns for systems containing oil, soap-solubilized water, and aliphatic or alicyclic alcohols as additives. A discussion of this work will be postponed to the section on the effect of additives. More recently, Mattoon and Matthews (141) have presented some qualitative results on systems of Aerosol OT (di(2-ethylhexyl) sulfosuccinate), *n*-dodecane, and water. For 15 per cent Aerosol OT in *n*-dodecane, the small-angle x-ray scattering intensity varied from weak to medium to strong as more water was solubilized up to the saturation point of 26 g. of water in 100 g. of soap solution.

Solubilization in ethylene glycol in which Aerosol OT, tetradecane-1 sodium sulfate, and undecane-1 ammonium chloride were the solubilizers has recently

been reported by Winsor (255) and is found to be distinguished from those systems in which water is the continuous phase by the absence in glycol-solubilized systems of anisotropic gelation which is found to occur in comparable water-solubilized systems. It is proposed that the hydrogen-bonded pseudo-ice structure in water is necessary for the adhesion between the units of dispersed phase without which gel structure cannot be evident. In both glycol and water solubilizing systems, it is not the unsolvated soap which is the mutual solvent but the liquid complex produced in the presence of the two immiscible liquids. When this point is considered, the apparent contradiction mentioned by Palit and McBain (184), between the effect of soaps on benzene-propylene glycol systems and the commonly accepted point of view on mutual solvents, disappears.

When to a homogeneous solution of triethanolamine oleate in paraffin oil increasing amounts of water are added, an inversion is found to occur (129). The various factors which bring about these reversible inversions, such as soap, water, and oil concentrations, additives, temperature, and solvent, have been more thoroughly studied qualitatively by Winsor (255).

V. EFFECT OF STRUCTURE OF SOLUBILIZER

There are a number of factors regarding the structure of solubilizers such as chain length, substitutions in the chain, and position of hydrophilic group, which would be expected to have some effect on solubilization. There have only been a few systematic studies made using fairly well characterized soaps and detergents and these data will be discussed. An attempt will be made to integrate various isolated data and indicate the effect of structural changes on solubilization. Soap solutions have lower solvent power for phenylazo- β -naphthylamine than do solutions of salts of paraffin-chain cations and more complex salts (157). Merrill (162) finds a less marked disadvantage of the soaps for *o*-tolylazo- β -naphthol, and Soldate (162) indicates that potassium oleate is much less effective than Aerosol OT as a solvent for propene vapor.

The enhancement in solubilizing power of cationic detergents over soaps of corresponding chain length has also been noticed in the case where dimethyl-aminoazobenzene was the solubilizate (125). Thus, for measurements at 30°C., the solubilizing power (grams of DMAB per mole of soap) was 4.32 at 0.4 M dodecylamine hydrochloride; 1.50 for the soap containing the same number of carbon atoms, estimated 2.1 for KC₁₃, the soap of the same length as the dodecylamine hydrochloride, and 2.71 for KC₁₄. It is of interest to note that the long x-ray intermicellar spacing of the C₁₂ cationic detergent is 69.9 Å. at 15 per cent, whereas the spacing for the same concentrations of KC₁₄ and KC₁₂ is 63.1 Å. and 54.2 Å. (72). These longer spacings would indicate a much larger micelle for the C₁₂ amine hydrochloride than for the corresponding fatty acid soaps and thus a much larger volume available for solubilization. Solubilizing power for hydrocarbons will always increase with increase in micellar size, although in certain instances it will decrease for polar compounds (115). Much further work is indicated for these systems to show whether there is much

more internal order in the anionics than in the cationics to account for this marked increase in solubilizing power.

A. EFFECT OF CHAIN LENGTH

The data in figure 8 and in table 2 show the effect of increase in chain length of potassium fatty acid soaps on the solubilization of ethylbenzene. It is to be noted that the increase in the rate of solubilization with soap concentration is consistent with the previous discussion concerning the loci of solubilization. It has been shown that there is only a very small decrease in C.M.C. with added hydrocarbon (116). It is possible then to plot the moles of ethylbenzene solubilized per 1000 g. of solution as a function of concentration of micellar soap. This is done in the case of the decanoate and the octanoate, the C.M.C.

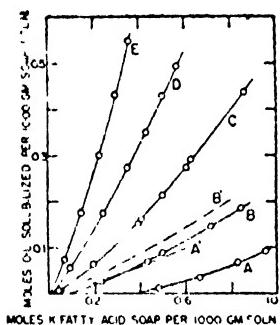


FIG. 8

Fig. 8. Solubilization of ethylbenzene in potassium fatty acid soaps (25°C.): (A) KC_8 , (B) KC_{10} , (C) KC_{12} , (D) KC_{14} , (E) KC_{16} . Dotted lines indicate solubilization by micellar soap.

Fig. 9. Effect of chain length of potassium fatty acid soaps (0.3 N) on solubilization of (A) dimethylaminoazobenzene, (B) *n*-heptane, (C) 1-octanol, (D) ethylbenzene, (E) 1-heptanol (75, 86, 125).

values of which are 0.095 M and 0.395 M , respectively. This serves to present a more accurate picture of the effect of chain length.

Further data have been reported on the effect of alkyl chain length on the solubilization of Orange OT (1-*o*-tolylazo-2-naphthol) by McBain and Johnson (152) and by McBain and Green (149), of DMAB (dimethylaminoazobenzene) (125), and of various long-chain alcohols (75). The effect of the number of carbon atoms in the colloidal electrolyte ion is seen to result in an increase in solubilizing power towards various solubilizates, as indicated in figure 9. Marked differences are noted in the relative solubilities of the added oils. The effect of structural changes of the solubilizate will be discussed in a later section under this heading. It is seen, however, that the most marked changes with chain length are found for hydrocarbon solubilizates and that with polar additives there appears to be a transition occurring. There have been no systematic data reported on the use of the fatty acid soaps with an odd number of carbon atoms for the solubilization

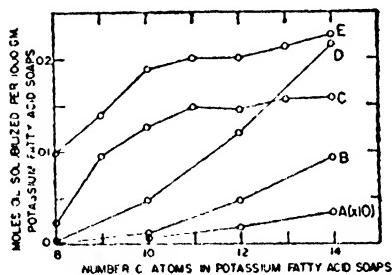


FIG. 9

of hydrocarbons. It appears that, when long-chain alcohols are the solubilizates, there is an inversion in solubilizing power which might be compared with various

TABLE 2
Solubilization of ethylbenzene in soap solutions (25°C.)
(Values corrected for water solubility)

MOLES OF SOAP PER 1000 G. SOLUTION	MOLFS OF MICELLAR SOAP PER 1000 G. SOLUTION	MOLES OF OIL SOLUBLE (S) PER 1000 G. SOLUTION	MOLFS OF OIL PER MOLE OF SOAP	MOLES OF OIL PER MOLE OF MICELLAR SOAP	VOLUME OF OIL SOLUBLE PER 1000 G. SOLUTION	MOLECULES OF OIL PER SOAP MICELLE (150 MOLECULES)
Potassium octanoate						
0	0	0.0016			0.196	
0.30	0	0.0012	0.004		0.147	
0.48	0.085	0.012	0.025	0.141	1.47	21
0.662	0.267	0.033	0.048	0.124	4.04	19
0.827	0.432	0.066	0.080	0.152	8.08	22
Potassium decanoate						
0.10	0.005	0.0014	0.014		0.171	
0.232	0.137	0.027	0.116		3.30	30
0.435	0.340	0.067	0.154	0.197	8.20	30
0.500	0.405	0.087	0.174	0.214	10.6	33
0.717	0.622	0.145	0.202	0.233	17.8	35
Potassium dodecanoate						
0.042	0.017	0.007	0.166	0.411	0.855	62
0.195	0.170	0.062	0.318	0.364	7.60	54
0.396	0.371	0.151	0.382	0.407	18.4	61
0.500	0.475	0.212	0.424	0.446	26.0	67
0.603	0.578	0.273	0.452	0.472	33.5	71
0.628	0.603	0.291	0.463	0.482	35.7	72
0.860	0.835	0.435	0.506	0.522	53.4	78
Potassium tetradecanoate						
0.096	0.090	0.054	0.563	0.600	6.60	90
0.242	0.236	0.176	0.728	0.745	21.6	107
0.347	0.341	0.272	0.784	0.798	33.4	120
0.432	0.426	0.348	0.807	0.817	42.7	123
0.500	0.494	0.427	0.855	0.866	52.3	130
0.566	0.560	0.492	0.872	0.888	60.3	133
Potassium hexadecanoate						
0.070	0.068	0.074	1.06	1.09	9.07	159
0.154	0.152	0.176	1.14	1.15	21.6	173
0.228	0.226	0.302	1.32	1.33	36.9	190
0.292	0.290	0.430	1.47	1.48	52.7	220

physical properties, such as melting point, of the fatty acids themselves. This transition in solubilization of the long-chain alcohols, however, may be ac-

counted for on the relative hydrophilic and hydrophobic character of these polar compounds and on the extent to which they penetrate into the palisade layer of the soap micelle (115). Winsor has suggested that this transition is between those relatively hydrophilic compounds whose solubilization is limited by the formation of a Type II system (S_2 micelles plus excess aqueous liquid) and those more lipophilic compounds whose solubilization is limited by the formation of a Type I system (S_1 micelles plus excess organic liquid) (255a).

A plot of the solubilization data of Kolthoff and Stricks (125) on DMAB shows that there is an almost linear increase in solubility with chain length or number of carbon atoms in the normal fatty acid soaps between C_{12} and C_{18} . The oleate values fall considerably below these curves, whereas the alkylamine hydrochloride (C_{12}) shows a stronger solubilizing effect when both are compared with soaps of corresponding chain lengths. There is an effect of branching noted in the use of Aerosol AY (diamyl sulfosuccinate), where the solubilizing power is much below that of the corresponding C_{14} soap (considering the length of the entire alkyl chain) and above that of the corresponding C_{10} soap (considering the length being equivalent to distance from terminal carbon atom to charged group).

The comparison above has included solubilization data for variation in chain length for the same family of compounds, the fatty acid soaps. It has been indicated that sodium and potassium soaps have the same C.M.C. values (110) as do the cetylpyridinium chloride and bromide (80) and sodium and potassium decyl and dodecyl sulfates (28, 110). Hartley (80) indicated that the ratio of solubilized azobenzene to cetylpyridinium is approximately constant over a wide range of concentrations. The constancy is not exact, and the ratio varies somewhat with the nature of the anion, indicating that the solvent power of the micelle is slightly modified by its ionic environment. Thus $\text{Br}^- > \text{Cl}^- > \text{SO}_4^{2-} > \text{OCOCH}_3^-$ in their solvent powers for azobenzene. The solvent powers of the micelles increase in the same order as do their sizes as deduced from mobility measurements (209). McBain and Green (149) report a considerable enhancement of solubility of Orange OT when sodium laurate is used in place of potassium laurate as the solubilizer. Thus at 25°C., 540 and 300 mg. of Orange OT are solubilized per liter of 0.3 M NaC_{12} and 0.3 M KC_{12} , respectively. These values are much larger than would be expected and are not at all of the minor order found for the cetylpyridinium salts. In addition, they find that sodium oleate solubilizes more Orange OT than does the potassium salt and that dodecylamine hydrochloride dissolves more than KC_{12} (66). Kolthoff and Stricks (125) find no differences in the solubility of Orange OT at 30°C. in NaC_{12} and KC_{12} , a result which is more in accord with the findings that the C.M.C. values of sodium and potassium fatty acid soaps are essentially equal (110, 125). In the solubilization of dimethylaminoazobenzene, sodium and potassium salts of C_{10} , C_{12} , and C_{14} fatty acids are found to be equal for each pair of equal chain length (125).

It has previously been reported that the C.M.C. values of various straight-chain soaps and detergents depend almost exclusively on the chain length (not

to be confused with the number of carbon atoms in the chain) and are relatively independent of the nature of the charged head (110, 201). However, a change from the chloride to the nitrate salt of dodecylamine has been shown to result in a decrease in solubility and in a change in C.M.C. from 0.014 *M* to about 0.01 *M* (200). Thus, a series of colloidal electrolytes such as potassium tridecanoate ($\text{CH}_3(\text{CH}_2)_{11}\text{COOK}$), dodecylammonium chloride ($\text{CH}_3(\text{CH}_2)_{11}\text{NH}_3\text{Cl}$), sodium dodecylsulfonate ($\text{CH}_3(\text{CH}_2)_{11}\text{SO}_3\text{Na}$), and sodium undecyl sulfate ($\text{CH}_3(\text{CH}_2)_{10}\text{OSO}_3\text{Na}$), all of about equal chain length (length between terminal carbon and ion charge), have approximately the same C.M.C., as can be seen in table 3. No systematic attempt has as yet been made to determine the effect of chain length rather than number of carbon atoms on solubilization. Various isolated data collected in table 3 indicate that solubilization values of polar compounds do not agree for solubilizers of the same chain length as do the C.M.C. Thus 0.3 *N* dodecylamine hydrochloride solubilizes 950 mg. dimethyl-aminoazobenzene (DMAB) per liter (125), whereas sodium tridecanoate would be expected to solubilize about 600 mg. (average value between 400 mg. for NaC_{12} and 800 mg. for NaC_{14}). The effect of polarity in the DMAB molecule may exert some influence on its solubility in the soap micelle. Hartley (80) has indicated that the solubility of azobenzene in soap micelles is considerably less than ideal when compared to its solubility in paraffins and more nearly approaches its behavior in some polar solvents. This would indicate a solubilization of azobenzene, in part at least, in the palisade layer of the soap micelle. This apparently is also true when the solubilities of various long-chain alcohols in KC_{14} and sodium dodecyl sulfate (75) (C.M.C. = 0.0066 *M* and 0.0058 *M*, respectively) and in KC_{12} and sodium decyl sulfate (118) (C.M.C. = 0.025 *M* and 0.023 *M*, respectively) are compared. In the first group the solubilities are different when the C_7 and C_8 alcohols are the solubilizates and are similar for longer alcohols. In the second group the values for the C_7 alcohol are different, whereas those for C_8 , C_9 , and C_{10} are about equal. This is of interest in the light of some recent work on the effect of various additives on the solubilization of long-chain alcohols (115). It was found that, when KC_{14} was the solubilizer, there was a transition in solubilization properties between C_8 and C_{10} alcohols. Similarly, when KC_{12} was the solubilizer, this transition was noted between C_7 and C_8 alcohols. The importance of these findings with relation to the effect of additives will be discussed below, but it is of some import to note that similar transitions occur in the solubilization of alcohols when the chain length of the solubilizer is considered. These transitions involve the solubilization of polar compounds in which the hydrocarbon portion of the solubilizate begins to overcome the contribution of the polar group to the solubility of the molecule. This depends not only on the extent of the nonpolar portion of the solubilizate, but also on the nature of the polar group and on the length of the solubilizer molecule. The solubilities of the much less polar compound, *n*-heptyl mercaptan, in KC_{12} and the decyl sulfate and in KC_{14} and the dodecyl sulfate are about equivalent, as would be expected if the idea of the transition phenomenon is correct. The solubilities of the typical hydrocarbon *n*-heptane are about equal in each group

TABLE 3
Effect of chain length on micellization and on solubilization
(0.3 N solubilizer)

TYPE OF DETERGENT	LONG-CHAIN GROUP	L	C.M.C.	#-Heptane	DMAB	C ₁₂ H ₂₄ SH	SOLUBILIZATION				C ₁₂
							A	moles/liter	moles/liter	mg./liter	
Fatty acid	n-C ₁₂ O ⁻	17.86	0.012	(0.07)*	(600)*						
Sulfonates	n-C ₁₂ OSO ⁻	18.43	0.010	0.077							
Sulfates	n-C ₁₂ OSO ⁻	18.19	(0.012)*	(0.075)*							
Amine hydrochloride	n-C ₁₂ NH ⁺	17.53	0.014	0.26	950						
Fatty acid	n-C ₁₄ O ⁻	19.13	0.0066	0.093	800	0.096	0.226	0.158	0.140	0.136	
Sulfates	n-C ₁₄ O ⁻	19.46	0.0057	0.101		0.0925	0.260	0.171	0.144	0.138	
Fatty acid	n-C ₁₆ O ⁻	16.59	0.026	0.043	400	0.0393	0.201	0.146	0.126	0.111	
Sulfates	n-C ₁₆ O ⁻	16.92	0.023	0.050		0.040	0.220	0.150	0.129	0.115	

* Values estimated from higher and lower detergents of the same type.

of anionic solubilizers of approximately the same length and C.M.C. That the addition of hydrocarbons has been found to cause only very small decreases in C.M.C. (116, 199), whereas the addition of alcohols and other polar additives results in considerable decreases in C.M.C. (26, 199), is a phenomenon which parallels the use of hydrocarbons and polar compounds as solubilizates.

It has been observed that the amount of 1-hexanol required to give an S₁ type system decreased for identical systems (although the detergent solutions were prepared on a per cent basis rather than on a mole basis) when sodium undecane-3 carboxylate, sodium undecane-3 sulfate, and undecane-3 ammonium chloride, respectively, were the solubilizers (254). This is in accord with the data in table 3 and with the aforementioned much larger intermicellar x-ray spacing observed in the cationies than in the anionies.

It has been inferred by Hartley (80) that the minor differences in the solubility of azobenzene in various cetylpyridinium salts varied somewhat as do the micelle sizes. If solubilization were to depend on micellar weight, then by the addition of a certain amount of added electrolyte, it would, for example, be possible to form micelles of a C₁₂ soap which would have a molecular weight equal to that of a C₁₄ or a C₁₆ soap. This is in accord with light-scattering results of changes in micellar weight with added electrolyte (33). However, while this increase in micellar size with added electrolyte would increase the solubility of the hydrocarbons, it would result in a marked decrease in the amount of polar compound solubilized (115). There are insufficient data on micellar weights at the present time to indicate whether micelles of the same molecular weight though of different chain length paraffin-chain ions would have equal solubilizing power for a hydrocarbon.

B. EFFECT OF SUBSTITUTION IN THE CHAIN

The replacement of a C—C by a C=C bond in the alkyl chain results in an increase in the C.M.C. value. Thus, the C.M.C. of potassium oleate has been found to be 0.0006 (30°C.) by solubilization measurements (125), 0.0007 0.0012 (25°C.) by the spectral dye method (28), and 0.0011 (25°C.) by refraction (109) as compared with values of about 0.0004-0.0008 (60°C.) (109, 227) for potassium stearate as determined by refraction and pH measurements. Solubilization data show corresponding decreases when the amounts of DMAB solubilized by potassium stearate and potassium oleate are compared (125). Since there is still considerable difficulty in the preparation of linoleic and linolenic acids of purity even up to 95 per cent, no valid solubilization data are available with the use of these solubilizers. Recently, a whole series of aryl and alkylated stearic acids have been prepared (230, 231), but no information as to the effect of substitution of this type on solubilization is available. Recently, the substitution of a hydroxyl group in the alkyl chain to form 9,10-dihydroxystearate has resulted in an increase in the C.M.C. (67), but no solubilization data are available with the use of this compound. Previously, Dreger, Miles, Ross, and Sheldovsky (41, 171, 218) in a series of papers described the preparation and surface and interfacial tension properties of a series of very interesting detergents in which

the charged head, the sulfate group, was systematically moved along the alkyl chain. Solubilization data on compounds of this type would be very interesting and, when obtained, will assist greatly in our complete understanding of the factors involved in micellization and in solubilization. Hartley (82a) has measured the interfacial activity of branched-paraffin-chain salts (sulfonated dialkyl esters of dihydric phenols) and found marked decreases in interfacial tension against various nonpolar liquids. However, evidences of typical micelle formation, such as the solubilization of azobenzene and changes in the equilibrium of suitably buffered indicators, were not observed. Winsor (254) has studied the effect of position and of type of charged group on solubilization and has found that, while the lipophilic solvent affinity of the *n*-alkyl group is essentially the same, the hydrophilic solvent affinity of the $\text{--SO}_4\text{Na}$ group diminishes markedly as its point of attachment to the *n*-alkane chain recedes from the terminal. Since there is a high degree of molecular order in solubilized systems, steric

TABLE 4

*Effect of position of $\text{--SO}_4\text{Na}$ group of *n*-tetradecane sodium sulfates on critical micelle concentration and on solubilization*

POSITION OF $\text{--SO}_4\text{Na}$	C.M.C. (1)	C.M.C. (2) STRAIGHT-CHAIN SULFATE	C.M.C. (2) C.M.C. (1)	⁽²⁾ CYCLOHEXANOL PER 10 ML CYCLO- HEXANE + 10 ML 20 PER CENT NaCl_4 SULFATE	
				ml.	(S) <i>n</i> -TETRADECANE SULFATE (S) BRANCHED SULFATE
	(moles/liter) $\times 10^{-4}$				
1	1.65	1.65	1.0	2.0-2.3	1.0
2	3.26	3.30	1.01	2.0	1.0
3	4.52	6.5	1.44	1.3-1.5	1.5
4	5.76	13	2.29	0.84-1.0	2.3
5	7.95	26	3.27	0.55-0.60	3.7
6	12.3	52	4.23	0.25-0.30	7.6
7	15.8	100	6.22	0.025-0.075	40

factors would be expected to be strongly influential in producing the above results.

Critical micelle concentrations in the tetradecane sulfate series increase as the point of attachment of the $\text{--SO}_4\text{Na}$ group on the *n*-alkane chain recedes from the terminal position (254). These concentrations were determined by the spectral dye method of Corrin and Klevens (28), which is a modification of the technique used by Sheppard and Geddes (223), and the increases noted were in accord with those changes seen in the surface tension curves on similar compounds (41, 171, 218). These data are given in table 4, as well as some comparable data on straight-chain alkyl sulfates of the same chain length (110). If only the straight-chain portion of the molecules is considered, it can be seen that substitution of only a methyl group on the α -carbon atom does not contradict the relationship which indicates that the C.M.C. depends on chain length and is virtually independent of substitution on atoms of the chain up to about 5 Å. from the charged head (110). This is in accordance with the data of

Ralston *et al.* (201), which show only minor changes in C.M.C. when groups containing up to three atoms are substituted for the amine hydrogens in the alkylamine hydrochlorides. It is evident from a comparison of the data in table 4 that the size and position of the alkyl side chain influence the total van der Waals attraction energy (necessary to overcome the repulsive energy of the like charged heads before micelle formation can start). The decrease in C.M.C. in comparing straight-chain and branched-chain pairs is not as large as has been observed upon the addition of long-chain alcohols, a result which would indicate a greater penetration of the alcohol into the palisade layer of the micelle than the branched chain which is, of course, held in position.

Although somewhat simpler solubility data, such as with heptane and 1-heptanol as solubilizate and additive, are not available, the effect of the position of the $-\text{SO}_3\text{Na}$ group in the detergent chain on solubilization can readily be advanced. The data in table 4 (255) indicate that there is a decrease in the amount of cyclohexanol required to dissolve cyclohexane in solutions of sodium tetradecane sulfates as the $-\text{SO}_3\text{Na}$ group is moved from position 1 to position 7. The important generalization which can be derived from these results is that the solubilization of organic compounds increases from the 1- to the 7-sulfate. With the use of *n*-alkyl soaps and detergents it has been found that as the C.M.C. decreases the solubilizing power of a system increases. However, it is seen that there is an increase in the C.M.C. with movement of the $-\text{SO}_3\text{Na}$ group from the 1- to the 7-position. When these values are compared with C.M.C. values of straight-chain sulfates (of chain length equivalent to maximum length up to $-\text{SO}_3\text{Na}$ in the branched-chain compounds), there is some enhancement over that of the corresponding nonsubstituted alkyl sulfate, owing to the presence of the branched chain which increases as the size of this branched chain increases. It has also been shown that there is a decrease in the solubilization of water as the $-\text{SO}_3\text{Na}$ in the tetradecane series is changed from the 1- to the 7-position (255).

A considerable amount of data has accumulated in the literature in which many of the commercial preparations of detergents have been used as solubilizers. As will be shown in a later section on additives, the addition of any compound which will reduce the C.M.C., such as electrolytes, amines, alcohols, etc., will also markedly effect the solubilizing power of a detergent. Thus, for example, in the preparation of an alkyl sulfate, the presence of any residual non-sulfated alcohol will result in a much more active solubilizer than if all the alcohol had been sulfated. The presence of electrolytes will result in a marked increase in the solubility of hydrocarbons and a marked decrease in the solubility of polar compounds (115). Some data using commercial preparations have recently been reported (125), and much more will be found in the work of McBain and his coworkers (144, 151, 157).

The solubilizing power on a weight basis of nonionic detergents such as carbowax and the polyethylene oxides has been found to be very weak (151). However, the condensation of a fatty acid radical or a substituted benzene ring on the end of the polyethylene oxide chain increases its solubilizing power. The complex

detergents such as hexanolamine salts of fatty acids have been shown by x-ray studies (206) and by osmotic behavior, conductivity, and viscosity to behave like colloidal electrolytes (65) but no systematic studies on pure preparations of this type of detergent have been reported. Many tables of solubilization of dyes such as Yellow AB and Orange OT are available (144), but since these solubilizers contain various additives or impurities only their relative solubilizing power is important. Solubilization data comparing hexanolamine oleate and two nonionic detergents, nonaethylene glycol monolaurate and a condensation product of (2-methylheptyl)phenol and ethylene oxide, called detergent "X," indicate that on a molar basis these detergents solubilize more than KC_{12} (163). Their C.M.C. values are also much below that of KC_{12} .

VI. EFFECT OF STRUCTURE OF SOLUBILIZATE

There are numerous factors with regard to the structure of the solubilizate which are seen to affect markedly the amount of solubilization of these compounds. The polarity, charge, molar volume, chain length, branching, substitution, planarity, etc. are found to be important in determining the degree to which these compounds will dissolve in the soap and detergent micelles. The physical state of the excess solute—solid, liquid, or gas—is an important factor in solubilization (255). In the solubilization of a solid compound the latent heat of fusion opposes the change of state from crystalline solid to solubilized or dissolved compound, and the ease of solubilization of a solid compound is therefore expected to be considerably less than that of the same compound existing as a supercooled liquid or of a closely related liquid compound. This would in part account for the much longer time required to dissolve solid polycyclics than liquid hydrocarbons (113) and would explain why the differences in the solubilities of liquid methylnaphthalene and naphthalene are much smaller than those between benzene and the alkylated benzenes (118). Winsor also indicates that the fugacity as well as the constitution of liquids forming the excess phase is of great importance in limiting their solubilization (255a).

A. EFFECT OF CHAIN LENGTH, CYCLIZATION, UNSATURATION, AND BRANCHING

For a particular preparation of soap or detergent, there are numerous examples of solubilization of families of compounds. As will be shown in the section on the effect of additives, the addition of an electrolyte, alcohol, amine, hydrocarbon, another soap, etc. will have some effect on the solubilization of various solubilizates. However, for any one preparation of solubilizer, it can be assumed that any differences in solubility will depend on the structure of the solubilizate, i.e., unless molecular interaction or specific binding occurs between one or more of the components in the system. Thus some indication of the effect of structure on solubilization can be gleaned from the very early work of Engler and Dieckhoff (50), as seen in table 5. Similar effects are noted in a study by Smith (225), in which the solubilization of various organic compounds in a commercial preparation of sodium oleate was investigated. Some of Smith's data are collected in table 6, where again some indications as to the influence of various factors such

TABLE 5

Solubility (ml.) of hydrocarbons in 100 ml. soap solution (room temperature) (50)

SOAP	BENZENE	TOLUENE	XYLENE	TURPENTINE
	ml.	ml.	ml.	ml.
Sodium oleate (10%)	10	9.6	7.4	7
Sodium palmitate (10%)*	1.8	1.3	1.4	0.4
Sodium rosin soap (15%)	8.8	8.2	8.0	11.2
Potassium rosin soap (15%)	8.4	8.0	6.8	9.0
Sodium stearate (10%)*	1.6	1.5	1.0	0.8
Sodium stearate (10%)* + 10 ml. phenol	9.2	13.9	37.0	101.0

* At elevated temperatures.

TABLE 6

Solubility of various organic compounds in 100 g. 0.4 N sodium oleate (225)

COMPOUND	SOLUBILITY	COMPOUND	SOLUBILITY
	grams		grams
Phenol	108	Methyl acetate	71
Cyclohexanol	59	Ethyl acetate	18.7
Aniline.	11.5	Carbon tetrachloride	20.6
		Chloroform.	6.65

TABLE 7

Effect of chain length, unsaturation, and cyclization on solubilization in 0.63 N potassium dodecanoate at 25°C.

COMPOUND	MOLAR VOLUME	SOLUBILITY IN MOLES PER LITER OF SOLUTION	VOLUME OF OIL IN MICELLES PER LITER OF SOLUTION	MOLECULES OF OIL PER MICELLE (150 MOLECULES)
n-Pentane	113.4	0.247	27.9	59
n-Hexane	131.5	0.178	23.2	42
Hexatriene		0.425		99
Benzene	88.5	0.533	47.2	126
Cyclohexane	104.5	0.430	45.9	102
n-Heptane	147.8	0.125	18.4	30
Toluene	107.0	0.403	43.7	96
n-Octane	163.1	0.105	17.2	24
Ethylbenzene	123.0	0.280	34.0	66
Styrene	120.0	0.332	39.6	78
n-Nonane	178.2	0.082	14.6	20
n-Propylbenzene	140.5	0.209	29.2	50
n-Decane	192.1	0.058	11.7	14
n-Butylbenzene	157.0	0.147	22.3	35
Naphthalene	112.2	0.042	4.7	10
Phenanthrene	174.1	0.0085	1.03	2.0
Fluorene		0.0056		1.3
Anthracene	142.3	0.00108	0.123	0.26

as polarity, unsaturation, and length of chain on solubilization are seen. Numerous other reports have dealt with similar structural aspects (75, 80, 113, 157, 161, 229). Recently, a number of attempts have been made to show more com-

TABLE 8

Solubilization of various hydrocarbons in 0.1 N detergent solutions at 25°C. (161)

COMPOUND	MOLECULAR WEIGHT	MOLAR VOLUME	SOLUBILITY IN WATER	AMOUNT SOLUBILIZED		
				KC ₁₂	NaC ₁₂	C ₁₂ HCl
			grams/liter	moles/liter		
<i>n</i> -Hexane	86	131.3	0.14	0.18	0.46	0.75
<i>n</i> -Heptane	100	147.1	0.05	0.12	0.34	0.54
<i>n</i> -Octane	114	163.3	0.02	0.08	0.18	0.29
<i>n</i> -Nonane	128	178.2		0.06	0.11	0.22
<i>n</i> -Decane	142	191.4		0.03	0.052	0.13
<i>n</i> -Dodecane	170	226		0.005	0.009	0.063
<i>n</i> -Tetradecane	198	261				0.008
<i>n</i> -Cetane	226	293.5				
2,2-Dimethylbutane	86	133.7		0.13	0.45	0.73
2,3-Dimethylbutane	86	131.1		0.14	0.46	0.75
2,3-Dimethylpentane	100	144.1		0.11	0.35	0.62
3,3-Dimethylpentane	100	115.1		0.10	0.31	0.55
2,2,4-Trimethylpentane	114	165.7		0.05	0.16	0.27
2,2,3-Trimethylpentane	114	160.4		0.09	0.18	0.30
Diisobutylene	112			0.10	0.38	0.43
Methylcyclopentane	94			0.032	0.26	0.40
Cyclohexane	84	108.5		0.23	0.56	0.87
1,2,4-Trimethylcyclohexane	126	160.0		0.012	0.012	0.019
Benzene	78	88.5	0.70	0.29	0.76	0.65
Toluene	92	106.7	0.49	0.13	0.51	0.49
Ethylbenzene	106	122.5	0.14	0.20	0.40	0.38
p-Xylene	106	123.5	0.13	0.20	0.36	0.34
p-Cymene	134	156.5		0.08	0.26	0.19
Amylbenzene	148	172.7		0.04	0.17	0.12

pletely the effect of various structural factors on solubilization (113, 161, 229). It can be seen from the data in tables 7 and 8 that:

1. Increase in the chain length of a normal paraffin or of an alkyl group on a benzene nucleus will result in a marked decrease in solubility.
2. Cyclization will result in enhanced solubility.
3. Unsaturated compounds will be more soluble than their saturated counterparts.
4. Branched saturated compounds have approximately the same solubility as their normal isomers.

These regularities start to break down in part when one considers the solubilization of polycyclic hydrocarbons. The presence of a second ring, as in the sub-

stituted biphenyl or, more particularly, in the simplest polycyclic, naphthalene, causes a change in the opposite direction so that these compounds are even less soluble than the normal paraffins of about the same molecular weight. Thus naphthalene is much less soluble than either *n*-decane or *n*-butylbenzene. It has also been found that tetralin and decalin are more soluble than naphthalene, with the decalin slightly more soluble than the other two compounds (118). Although cyclohexane is less soluble than benzene, owing probably to the more polar, partial double bonds of the latter compound (also possibly owing to the smaller size of the benzene molecule), it is more soluble than the linear *n*-hexane.

TABLE 9
Solubility of various polycyclic hydrocarbons in 0.5 M KC₁₂ at 25°C.
(Corrected for water solubility)

COMPOUND	MOLECULAR WEIGHT	GRAMS OF OIL PER LITER OF SOLUTION	(<i>N</i>) MOLES OF OIL PER LITER OF SOLUTION ($\times 10^3$)	LOG <i>S</i>	MOLECULES OF OIL PER MICELLE
Benzene	78.05	30.6	391	-0.41	118
Ethylbenzene	106.08	22.0	208	-0.68	63
<i>n</i> -Butylbenzene	134.11	14.9	112	-0.95	33
Naphthalene	128.16	4.26	33.3	-1.48	10
Acenaphthene	154.20	1.00	6.48	-2.19	2.0
Fluorene	166.21	0.728	4.38	-2.36	1.3
Phenanthrene	178.22	1.21	6.65	-2.18	2.0
Anthracene	178.22	0.155	0.85	-3.07	0.26
Fluoranthrene	202.24	0.578	2.86	-2.54	0.86
Pyrene	202.24	0.453	2.24	-2.65	0.68
Chrysene	228.28	0.143	0.627	-3.20	0.19
1,2-Benzanthracene	228.28	0.145	0.635	-3.20	0.19
Triphenylene	228.28	0.0765	0.336	-3.47	0.10
Naphthacene	228.28	0.023)*	(0.10)	(-4.0)	(0.030)
Methylcholanthrene	248.34	0.087	0.323	-3.49	0.10
1,2,5,6-Dibenzanthracene	278.33	0.024	0.0862	-4.06	0.026

* Approximate value.

As the size of the solubilizate is increased by annelation (ring closure), the solubilities of these polycyclics decrease markedly, as the data in table 9 indicate (113). The relationships which hold for the solubilization of the more simple hydrocarbons cannot be extended to these complex polyacenes. A possible explanation for this may be found in the fact that much larger micelles are necessary to solubilize these polycyclics. Thus, whereas more than one molecule of the simpler compounds can be solubilized per micelle of 150 soap molecules, as seen in table 7, only a fraction of one polycyclic molecule would be soluble in micelles of this size. (A value of 150 soap molecules per hydrocarbon-swollen micelle is an average value of a number of different calculations for a soap of this chain length: (1) a value of 140 as calculated from x-ray evidence of swollen micelles (143), in which it is indicated that swollen micelles have about twice the

number of soap molecules as the hydrocarbon-free micelles; (2) one of 130 calculated from equations describing the size of swollen micelles (110), using as a basis the molecular weight values of nonswollen micelles as determined by light scattering (32); and (3) one of 140-160 as obtained from preliminary light-scattering measurements on hydrocarbon-swollen micelles (118).) Since the solubilization of hydrocarbons has been shown to involve the presence of a suitable hydrocarbon-like atmosphere, it is not necessary to postulate another mechanism of solubilization for the polycyclics and similar very insoluble molecules. Rather it should be sufficient to recognize the fact that each molecule of dibenzanthracene, for example, requires a certain critical volume of hydrocarbon atmosphere for its solubility. This atmosphere can only be supplied by a large aggregate of soap molecules. The smaller aromatics and simpler hydro-

TABLE 10

*Probable minimum size of micelle necessary for solubilization of polycyclic hydrocarbons
(N = number of soap molecules per micelle)*

COMPOUND	MOLECULES OF OIL PER 150-MOLECULE MICELLE	N	D
Benzene	118	150	60
Naphthalene	10	150	60
Acenaphthene	2.0	150	60
Phenanthrene	2.0	150	60
Anthracene	0.26	600	120
Fluoranthrene	0.86	175	65
Pyrene	0.68	220	73
Chrysene	0.19	790	138
1,2-Benzanthracene	0.19	790	138
Triphenylene	0.10	1500	190
Naphthacene	0.030	5000	360
Methylcholanthrene	0.10	1500	190
1,2,5,6-Dibenzanthracene	0.026	6000	390

carbons need a much smaller volume of hydrocarbon per solubilized molecule and thus many more can fit into a single swollen micelle. The data in table 10 indicate the probable minimum size of micelle necessary for the solubilization of polycyclic hydrocarbons (113). Whether micelles of this magnitude are possible has not been experimentally verified, but it has been indicated that micelles of some 1000-2000 molecules exist at low soap-high electrolyte concentrations (34) and it has been indicated that at higher soap concentrations the size of the micelle is larger than at lower concentrations. As the soap concentration increases, there is effectively less free volume between neighboring micelles and the ionic atmosphere around one micelle may be affected by those of its nearest neighbors. Experimentally, as seen in figure 6, this is indicated by an increase in the rate of solubilization of hydrocarbons with soap concentration as well as by a decrease in this rate when polar compounds are the solubilizates (115).

1. Effect of molar volume

X-ray measurements of potassium laurate solutions indicate that the chemical nature of the solubilizate markedly affects the change in long spacing (72, 74, 97, 150). When the change in spacing expressed in Ångström units per mole of additive per mole of soap is plotted against molar volume of liquid two straight lines are obtained, one for normal paraffins, the other for alkylbenzenes, as seen in figure 10, which extrapolate to about 50 ml. per mole or 4.4 Å.³ per molecule (97). The micelle aggregates are here considered to consist of at least five double layers of soap molecules oriented side by side and tail to tail. On the basis that the oil is layered between the ends of the hydrocarbon tails of the soap molecules in the micelle, the extrapolated lines should begin at the origin. Thus a portion

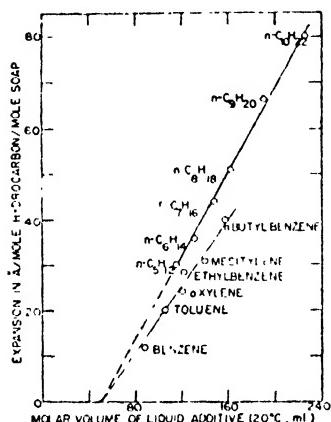


FIG. 10

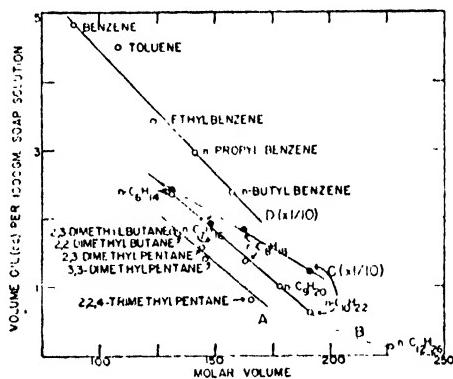


FIG. 11

Fig. 10. Change in micelle repeat distance of 22.1 weight per cent potassium dodecanoate solutions with molar volume of additive (97).

Fig. 11. Effect of molar volume of various paraffinic hydrocarbons and alkylated benzenes upon solubilization in (A) 0.1 M, (B) 0.1 M, (C) 0.63 M, and (D) 0.63 M potassium dodecanoate solutions (86, 161, 229).

of the solubilized additive is adsorbed elsewhere, perhaps between the side of the hydrocarbon chain in the soap palisade layer or, as will be seen in a later discussion, perhaps the model used by these investigators is in error.

Following these findings that the long x-ray spacing varies with molar volume of additive, attempts have been made to show how molar volume as well as other factors influence solubilization (113, 161, 229). McBain and Richards report that solubilization appears to fall off linearly with molar volume and then to decrease more slowly for larger molecules ($C > 10$) and that the more highly branched compounds are more soluble than straight-chain paraffins of the same molecular weight (161). However, this is not borne out by their data, for the values of grams of oil per 100 ml. of soap solution are 0.64, 0.63, 0.64 for *n*-hexane and the 2,2- and 2,3-dimethylbutanes; 0.54, 0.63, 0.55 for *n*-heptane and the 2,3- and 3,3-dimethylpentanes; and 0.33, 0.30, 0.34 for *n*-octane and the 2,2,4-

and 2,2,3-trimethylpentanes, respectively. A plot of their data showing grams of oil solubilized per 1000 g. of 0.1 *N* KC₁₂ solution as a function of molar volume shows this reported linearity, but this plot must be made using volume instead of weight of solubilizate. When this is done, curves similar to those in figure 11 are obtained. It can be seen that two lines must be drawn through these data, one for the normal paraffins and the other for their highly branched isomers. When solubilization data at higher KC₁₂ concentrations, 0.63 *N*, are included (113, 229), it is seen that this linearity carries over to the alkylbenzene series and that there is a difference in the slopes of the alkylbenzene and normal paraffin series which is consistent with the x-ray data. There are also differences observed in the slopes of the data for normal paraffins at the two concentrations (0.1 *N* and 0.63 *N*) of KC₁₂. This can be explained on the basis that the maximum rate of increase of solubilization is not reached in KC₁₂ until about 0.15 *N*.

Figure 11 shows that as the solubility of a hydrocarbon decreases, as in the case of *n*-decane, the linearity of volume of oil vs. molar volume no longer holds and the solubility approaches asymptotically a zero value. On this basis, the plots of log solubility as a function of molar volume of the polycyclic hydrocarbon solubilities are seen to have some validity (113). Two linear plots were necessary for the polycyclic data,—one for the linear polyacenes, the other for the nonlinear polycyclics. This is in accord with the treatment of the paraffin data in figure 11, where two curves are found to be necessary to fit the linear and the nonlinear data.

2. Apparent densities of solubilized oils

In the light of the discussion in the last few paragraphs, the reported changes in density of KC₁₂ solutions to which *n*-heptane and triptane (2,2,3-trimethylbutane) (73) and ethylbenzene are added (229) is of interest. These solubilizates show a linear change in apparent density with increase in concentration of added oil. The first and last oils have apparent densities much higher than their bulk densities when the concentration of added hydrocarbon is small and approach their bulk densities with saturation. This might be expected if the center of the spherical or oblate spheroid micelle is considered to be filled by hydrocarbon-like solubilizates before the micelle takes on its most normal configuration in which there is a minimum of strain, e.g., a spherical swollen one if the oblate spheroid is the nonswollen micelle. Triptane, on the other hand, has an apparent density in low solubilizate concentrations about equal to its bulk density and a much higher apparent density near saturation. It is apparent that more information will be necessary before speculation on this finding is advanced, particularly to determine whether the division of properties of normal paraffins and branched-chain hydrocarbons as seen in figure 11 will carry over to these measurements.

B. POLARITY OF THE SOLUBILIZATE

The differences in x-ray spectra, rates of solubilization with increase in soap concentration, the discussion of types and mechanism of solubilization, as well as some of the data shown in tables 5 and 6, indicate that the presence of a polar

group on the solubilizate will have a marked effect on its solubility. The very early work of Engler and Dieckhoff (50), as well as the later work of Smith (225), indicates in a qualitative manner that the polarity of the molecule influences the solubilizing power of a particular system. The marked differences in the solubilization of hydrocarbons and their polar counterparts will be illustrated most strikingly in a later section on additives, in which the simultaneous solubilization of polar and nonpolar compounds (114) and the effect of various electrolyte additives on the solubilization of both types of solubilizates (115) will be discussed. The formation of mixed soap micelles, as is indicated by a decrease in the C.M.C. when a soap of a lower C.M.C. is added to a more soluble soap (105), must be considered to be due to a solubilization of the less soluble soap by the more soluble one. As mentioned previously, soap mixtures of KC_{12} and KC_{14} , of NaC_{12} and NaC_{16} (220), of Na and CaC_{12} sulfate, and of Na and

TABLE 11

Solubilization of various polar compounds in 0.1 N detergent solutions at 25°C. (158)

COMPOUND	MOLECULAR WEIGHT	MOLAR VOLUME	SOLUBILITY IN WATER	AMOUNT SOLUBILIZED		
				KC_{12}	NaC_{12}	$C_{12}HCl$
			grams/liter		moles/liter	
Methyl <i>tert</i> -butyl ether.....	88	118	51.26	1.66	2.20	2.05
Methyl <i>tert</i> -butyl ketone.....	100	125.0	18.20	1.20	1.82	1.78
Amyl acetate	116	134.1	1.73	0.89	1.71	1.45
Isopropyl <i>tert</i> -butyl ether.....	117	157.3	0.50	0.14	0.73	0.53
Octylamine.....	129	166.0	0.20	0.07	0.07	0.13
<i>n</i> -Octyl alcohol.....	130	157.8	0.59	0.29	0.59	0.18
2-Ethyl-1-hexanol	130		0.13	0.064	0.47	0.36
Dodecanol.....	158	191.7		0.03	0.13	0.052
Oleic acid.....	290	339.6		0.018	0.05	0.024
Tributyrin.....	302	295.7		0.11	0.37	0.22

CaC_{12} sulfonate (233) should be considered to involve a polar type of solubilization in which the less soluble soap is solubilized by the more soluble one (111). The rates of solution of one soap in another have been studied by Shedlovsky, Miles, and Scott (220).

The results of solubilization of a series of polar compounds by three different solubilizers are shown in table 11 (161). It is interesting to note that whereas the solubilizing power for hydrocarbons was C_{12} amine hydrochloride > sodium oleate > KC_{12} , the order now is sodium oleate > $C_{12}HCl$ > KC_{12} , which would indicate a rough correlation between chain length and volume available for solubilization in the region of the palisade layers of the two-layer soap micelle. These authors compare the solubilization of polar and nonpolar compounds and indicate that molar volume is apparently not generally applicable to all types of compounds. Of course, it must be recognized that molar volume-solubility relationships can only hold for solubilization in the hydrocarbon center of the micelle. As will be shown later, the degree of polarity or hydrogen-bonding

capacity determines the position of the polar compound in the palisade layer of the micelle and thus controls the volume available for the solubilization of these solubilizates (114).

Ward considers that the lower alcohols are held predominantly in the micelle surface (247), and Angelescu and Manolescu consider that phenols are similarly located or even oriented outside the micelles (4). For alcohols up to C₃ which are quite miscible with water, it cannot be determined whether there is a distribution of alcohol molecules which favors penetration into the palisade layer. However, with longer chain alcohol additives, a decrease in C.M.C. is observed, the decrease being larger with increase in chain length of the additive (26). It has also been observed that, for equal chain length of additive, the C.M.C. will decrease more with decrease in the hydrogen-bonding capacity or polarity of the additive (118). Thus *n*-butylamine, for example, will decrease the C.M.C. value

TABLE 12

Solubility of normal primary alcohols, amines, and mercaptans in solutions of 0.3 mole per 1000 g. solution

(Solubility in moles per 1000 g. soap solution)

SOAP	KC ₄	KC ₆	KC ₁₀	KC ₁₁	KC ₁₂	KC ₁₃	KC ₁₄	NaC ₁₂ SULFATE
<i>Alcohols:</i>								
C ₇ H ₁₆ OH	0.099	0.139	0.188	0.201	0.201	0.212	0.226	0.260
C ₈ H ₁₇ OH	0.023	0.095	0.127	0.148	0.146	0.156	0.158	0.171
C ₉ H ₁₈ OH	0.004	0.076	0.0965	0.1165	0.126	0.132	0.140	0.144
C ₁₀ H ₂₁ OH	0.003	0.063	0.0923	0.104	0.111	0.122	0.136	0.138
C ₁₁ H ₂₃ OH	0.003	0.072	0.0865	0.107	0.1075	0.116	0.114	0.125
C ₁₂ H ₂₅ OH*	0.002	0.056	0.0840	0.0870	0.082	0.077	0.034	0.123
<i>Amine:</i>								
C ₁₀ H ₂₁ NH ₂	0.004	0.102	0.11	0.113	0.113	0.113	0.119	0.110
<i>Mercaptan:</i>								
C ₇ H ₁₆ SH	0.0007	0.0014	0.0102	0.0171	0.0393	0.0591	0.090	0.0925

* Values taken from figures (75).

of a number of detergents more than an equal concentration of added C₄ alcohol. Transition effects, the importance of which has only recently been noted (115), are also seen in the small changes observed in C.M.C. with amphipathic additives which approach in size that of the colloidal electrolyte (199).

The solubility of polar compounds in salt-free soap solution is much greater than that of the corresponding hydrocarbons (75, 115). The effect of an increase in concentration of the solubilizer is seen in figure 6, which is typical of these systems. Recently a systematic study was made by Oppenheimer (75), in which he varied both the length of the potassium fatty acid soap and the alcohol chain. These results are collected in table 12. A number of interesting conclusions can be drawn from these data:

1. A general increase in solubility of alcohols with chain length of the soap is seen, with the greatest increase between C₈ and C₉ soaps, except for 1-heptanol. The decrease in the C.M.C. of the C₃ soap from its alcohol-

free value of 0.39 M (109) may not be very much when the additives are equal to or longer than the soap molecule (199), and thus very little micellar soap would be available for solubilization in these experiments where 0.3 M is the concentration of solubilizer. The C.M.C. values of the C_9 and C_{10} soaps are 0.20 M and 0.095 M, respectively, and thus smaller changes in solubilization would be expected in going from C_9 to C_{10} soaps. A comparison of the type made in figure 8 and in table 2, where corrections are made for nonmicellar soap, is not possible when alcohols are the solubilizates because the C.M.C. values are not known for long-chain alcohol additives.

2. A decrease in solubility with number of carbon atoms in the alcohol chain, with the greatest decrease between C_7 and C_8 alcohols, is noted.

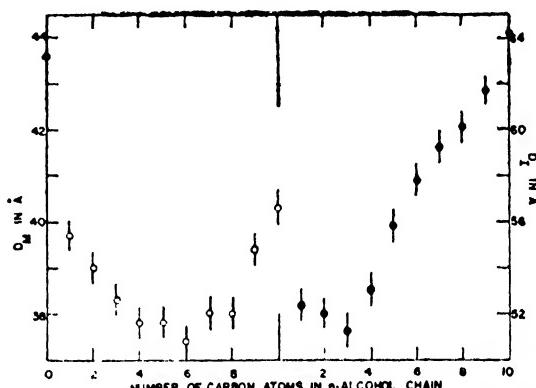


FIG. 12. The effect of normal alcohols on the diameter of micelles (D_M) and on the long (intermicellar) spacing (D_I) of 1.02 M sodium dodecyl sulfate solutions (74).

3. It appears that as more penetration into the palisade layer occurs, owing either to an increase in the chain length of the alcohol or to a decrease in the polarity by going from $-OH$ to $-NH_2$, some transition occurs as is evidenced by a leveling off of solubility values in the C_{10} amine and C_{11} alcohol with increase in chain length of the soap. A complete reversal is observed in the C_{12} alcohol, in that there is initially an increase in solubility with increase in length of soap molecule followed by a decrease with further increase in the number of carbon atoms in the fatty acid soap.

More data as to the effect of variations in concentration on the solubilization of these alcohols are necessary before these interesting results can be fully interpreted from a mechanistic point of view. In this connection, figure 12, which shows the changes in the long x-ray spacings, D_I , and in the micellar spacing, D_M , of sodium dodecyl sulfate with added alcohols (74), is of some interest in indicating the loci of solubilization of these solubilizates. In the case of solubilization of dimethyl phthalate, the lack of an increase in D_I was interpreted as indicating the adsorption of these additives on the micelle surface (150). It would appear that polar, and particularly amphipathic, molecules are

likely to be oriented in the surface region of the micelle aggregate. Since the diameter of the latter is only of molecular dimensions, it is expected that orientation will have a very great effect on solubility and that this orientation will be an important factor in the changes observed in the x-ray spectra of alcohol-soap systems. The increase in long x-ray spacing with added long-chain alcohols would appear to indicate solubilization in the micelle center. However, the changes in micellar spacing indicate some decrease with added alcohols, a result which is to be expected if palisade penetration is the mechanism involved in solubilization of this type. The importance of these results in the interpretation of micellar structure will be discussed in a later section.

VII. TEMPERATURE EFFECTS

It appears that most factors which decrease the C.M.C. and increase the size of the micelle will result in an increase in the solubility of hydrocarbons and usually in that of polar compounds. Thus, increase in chain length of solubilizer, the use of many additives (salts, other soaps, alcohols, amines, etc.), as will be seen in the following section, and decrease in temperature result in decrease in C.M.C., increase in micellar size, and usually increase in solubilizing power. Thus it has been shown (109) that for each member of an homologous series at a constant temperature, if the C.M.C. is known for any member:

$$\log \text{C.M.C.} = A + BN$$

where N = number of carbon atoms in the chain, B = an empirical constant (may be taken to be $\log 2$ with sufficient accuracy), and A = a constant for the particular temperature and homologous series, which may be determined from a known value of the C.M.C. for one member of the series. The constant B has recently been shown by Debye (32) to be a factor in the energy function associated with attractive forces resulting in micelle formation. The increase in solubilization with increase in length of soap chain has been shown above and light-scattering measurements have indicated a corresponding increase in micellar size (32). By means of the spectral dye method (28) applied to soap-salt systems (27) and by refraction measurements (106, 109) it has been shown that the log of the C.M.C. of anionic soaps is linearly dependent on the log of the cation concentration of added salt and is independent of the nature of the salt anions. These results are in essential agreement with the surface tension and interfacial tension measurements of Powney and Addison (191), who studied the change in C.M.C. of dodecyl sulfate solutions containing various concentrations of added sodium chloride and calcium chloride.

Various results have been reported regarding the effect of temperature on the C.M.C. From conductivity measurements of sodium alkyl sulfonate solutions by Wright *et al.* (256), of alkylamine hydrochlorides by Ralston and Hoerr (202), from refraction measurements on some soaps and alkyl sulfonates (109), as well as a number of other measurements, it has been shown that the C.M.C. increases slightly with increasing temperature. Bury and Parry (19), from density measurements on KC_{12} solutions, indicate that the C.M.C. decreases with

increase in temperature, and Ekwall finds that the C.M.C. of some fatty acid soaps is independent of temperature (46). Brady and Huff (16) report an initial decrease in C.M.C. followed by an increase above 45–50°C. The application of the spectral dye method to temperature effects indicates that the C.M.C. decreases with increasing temperature, but these results have been shown to be a property of this particular method (107). From the solubilization of dyes with detergents, Kolthoff and Stricks (125) find that the addition of salt has little effect on the C.M.C. values at elevated temperatures. This result does not agree with that obtained by Wright *et al.* (256), who conclude from conductance measurements of sodium dodecylsulfonate solutions in the presence of added sodium chloride that the effect of the sodium ion on the lowering of the C.M.C. decreases considerably with rise in temperature.

TABLE 13
Temperature and salt effect on solubilizing power
(Grams of dimethylaminobenzene per mole of soap) (126)

TEMPERATURE	Caprate	Detergent								C ₁₂ amine hydrochloride			
		Laurate				Myristate				Oleate		At 0.4 M	
		No salt	1.0 N NaCl	No salt	1.0 N KCl	No salt	0.5 N KCl	No salt	0.05 N KCl	No salt	0.05 N NaCl	No salt	0.05 N NaCl
°C.													
50	1.19	0.95	2.43	2.16	4.15	4.87	5.72	5.63	5.9	3.30	3.9		
30	0.64		1.50	1.55	2.71		3.24	3.30	4.32		2.23	3.35	
Ratio: 50/30	1.86		1.62	1.39	1.53		1.76	1.3			1.5	1.16	

The change in solubilizing power with temperature is seen in table 13 for the case of solubilization of dimethylaminobenzene (DMAB). It is apparent that the ratio of the solubilizing power of a soap with temperature is different for different soaps. It has also been observed that, at least in the solubilization of dyes, the solubilizing power depends also on the structure of the molecule which is solubilized (66, 125, 149). Lambert and Busse (130, 131) have indicated that the use of 50°C. temperatures for solubilization would decrease the time necessary to reach equilibrium from a number of days to as little as 15–30 min. and the resulting values of solubilizing power would not be affected by the use of this higher temperature. This would appear to be a contradiction of the previous results. It is seen that in the solubilization of DMAB (table 13) and for other dyes (126) (Orange OT and azobenzene) the ratio of the solubilizing power is usually lower in the presence of electrolytes and the solubilizing power is increased with increase in temperature.

The reported increase in solubility with temperature in these systems is in accord with the effects of temperature which are noted in normal solubility phenomena in which paraffin-chain salts are not the solvent. In these latter systems, the increase in temperature results in an increase in molecular dis-

persion of the solute, owing to increased thermal motion and a corresponding increase in the wetting of the solute by the solvent molecules. It is probable that the enhancement in solubility of DMAB in the presence of paraffin-chain salts is due in part to this normal temperature effect rather than to a specific increase in the solubilizing power of the soaps. The finding by Debye (33) that the molecular weight of a micelle of trimethyldodecylammonium bromide decreases just as the C.M.C. increases with increase in temperature lends support to this contention. This decrease in micellar weight would be expected to result in a decrease in solubilizing power rather than in an increase. It will be shown later that the effect of added electrolytes on the solubilization of DMAB (126) is similar to that observed when long-chain alcohols are the solubilizates (115), indicating that the solubilization of DMAB is probably of the polar type in that this substance is solubilized in the palisade layers of the soap micelle.

The anomalous effect of temperature on solubilization in various systems has been discussed from the point of view of its effect on the miscibility of the organic liquid (single compound or mixture) and aqueous liquid (water or salt solution) as separated from the effect on the amphipath (255). When the amphipath is an alkali metal salt, a rise in temperature usually diminishes the solubilization of organic liquids in micelles in which polar groups are oriented outward and results in an increase in the amount of water or other polar liquid solubilized in those cases where one has a system of inverted micelles (polar groups oriented toward micelle center). However, many exceptions to these regularities have been observed, particularly in the first type of systems.

VIII. EFFECT OF VARIOUS ADDITIVES

There is a very considerable literature, both in journal reports and in patents, concerning the effectiveness of a whole series of builders or additives which enhance the detergent action of all types of surface-active agents. The role of detergency involving removal of dirt and solubilization of this dirt by higher concentrations of soaps has been discussed by McBain (144) and the relationship between detergent action and solubilization has been also reviewed by Preston (192), who summarized the many radical property changes which occur at the C.M.C. Summaries of the aspects of detergency and the function of various additives have been published by Aickin (2), Sisley (224), and Chwala and Martina (21). Goette has indicated that the cleansing action of a solution of NaC_{12} sulfate can be increased by adding a certain amount of any neutral salt but that if this optimal amount is exceeded, the cleaning action is retarded (64). The phenomenon of solubilization and the role of soaps and detergents in the presence of various additives in the light of textile processing have been recently reviewed (29). The action of added electrolytes on the C.M.C. of soaps has been shown to depend on the number of equivalents of added cations and is independent of the nature of the anion (27, 109). However, it has been found that the optimum cleaning action of a liquid, at concentrations below the C.M.C., will be reached at a lower equivalent concentration of sodium pyrophosphate than by adding sodium sulfate and this latter requires a lower

concentration than sodium chloride (2, 78, 186). Similarly, in contrast to the effect of various additives on the C.M.C., potassium ferrocyanide has been found to be less effective than potassium sulfate, potassium sulfate less than potassium chloride, and potassium chloride less than sodium chloride, all in equivalent amounts, in increasing the solubility of various hydrocarbons (115, 229). Just the opposite has been found to occur in the solubilization of polar compounds, a result which indicates very definitely the presence of at least two loci of solubilization in the soap micelle (115). These findings would appear to indicate a more direct relationship between detergent and solubilization properties in the presence of various additives, whereas detergent action, C.M.C., and solubilization can be related in the absence of these additives. This latter relationship has been reviewed by Preston (192), but it is seen not to be valid in the presence of added electrolytes.

Various mixtures have been prepared for specific purposes. Thus a soap composition suitable for use in hard water and sea water is described in typical vague terms as being composed of a water-soluble soap and a mixture of alkyl derivatives of an aromatic (not more than two benzene nuclei) sulfonate (51). An improvement in detergent action is claimed for the use of small amounts of a C₁₀-C₁₄ fatty acid nitrile of *N*-acetylmorpholine, or of hydroxy acid amides as additives to water-soluble salts of alkylsulfonic acids (240). A recent summary discusses the effect of mixtures and impurities or additives on the properties of various commercial preparations of detergents (52). Tests such as lowering of surface tension, foaming, detergency, and wetting time by the canvas disc method have been used to show the effect of valency of additives, using various alkyl sulfates (41). Harris (76, 77) has recently reviewed the effect of electrolyte builders or additives for surface-active agents. The addition of electrolytes reduces surface and interfacial tensions, reduces critical conductivity, improves wetting speeds, and enhances detergent action. The valence of the additive has marked effects on these properties, since much smaller amounts of polyvalent ions are required to produce a given change in property. Excessive amounts beyond the optimum generally result in significant decreases in surface activity.

The above indicates in brief that the emphasis on builders or additives has been for the main part from the point of view of application. The importance of the part played by solubilization in detergency has been discussed by McBain (144) and as a transition factor in emulsification by Schulman *et al.* (210, 215). The marked increase in the past few years in reports concerned with additive effects can, of course, be correlated with the preparation of a host of new detergents, some of very interesting structural properties. Since by far most of these are commercial preparations, their descriptions and properties have not reached the academic literature. When they have been studied, "technical preparations have most often been used and too little help seems to have been given by the preparative chemist to his physical colleague—a state of affairs which could be remedied by more preparative activity on the part of the latter" (84).

Many additives have been shown to influence both C.M.C. and solubilization. The addition of a more soluble soap in large concentrations will increase the

C.M.C. and decrease the solubilizing power, whereas when a soap of a longer alkyl chain or a less soluble one is added the opposite effects are noted if, of course, the same cation is present (105, 109, 117, 229). The addition of long-chain alcohols and amines will greatly enhance the solubilization of hydrocarbons, and the presence of solubilized hydrocarbon will enhance the solubility of polar compounds (114). Weichherz (248) has shown that the addition of phenol to soap in benzene solution is necessary for the solubilization of water, and Pink (187) indicates that the addition of 1.1 g. phenol to 3.4 g. ethanolamine oleate in 39 g. benzene increases the solubility of water from 0.45 ml. to 5.2 ml. The addition of 1.5 g. cresol results in a similar increase. The addition of electrolytes produces complex effects which depend on various factors such as the nature of the solubilizer, its concentration, the polarity of the solubilizate, the type of electrolyte, etc. (66, 80, 115, 126, 149, 161, 229, 254). Various complex additives such as the sodium carboxymethylcelluloses have been shown to enhance detergent properties considerably (9, 96, 243) but, as yet, no solubilization data are available concerning this type of additive. The addition of carboxymethylcellulose to KC_{12} solutions results in a decrease in C.M.C. similar to that observed when equivalent amounts of other electrolytes are added (169).

1. Solubilization by soap mixtures

It is now recognized that the solubilizing power of a soap or detergent will decrease and the C.M.C. increase as the purity of the preparation is increased. This is, of course, valid only if the impurity is a soap of longer chain length (lower solubility). Thus the defatting power and turbidity point of a fatty acid sulfate were reduced by the addition of increasing amounts of C_6 C_{11} sulfates (53). Commercial soap mixtures, even those free of electrolyte and unneutralized fatty acids, are excellent solubilizing agents, for the lower soaps solubilize the normally insoluble longer chain soaps and because of this their solubilizing power is enhanced. However, to understand better the various factors involved in solubilization with soap mixtures, it has been necessary to prepare mixtures of known composition.

Various phenomena related to solubilization, such as changes in the long x-ray spacings (72) and in C.M.C. (105, 109), are included in figure 13, which shows also the effect of various soap mixtures on the solubilization of ethylbenzene (229) and *n*-heptane (117). It is seen from the linear changes with mole fraction that there is a direct correlation in the change in long x-ray spacing and the amounts of ethylbenzene and *n*-heptane solubilized, indicating a constant volume available for saturation with hydrocarbon. The nonlinearity of solubilization in various mole fractions of KC_{11} and KC_8 is due in part to the fact that the total concentration is 0.1 *M*, well below the C.M.C. of 0.395 *M* for the KC_8 (109). However, there is some enhancement in the solubility of ethylbenzene in KC_{11} , since the shorter chain soap acts like a salt which depresses the C.M.C. and correspondingly increases its solubilizing power.

Another approach to the effect of soap mixtures is indicated by the data in figure 14 (117), in which the effect of varying concentrations of soap of different chain lengths added to 0.35 *M* KC_{11} is seen. There is the usual enhancement in

concentration when the same soap, KC_{14} , is the additive. The added KC_{16} , normally insoluble at room temperature, is found to be readily solubilized by KC_{14} and greatly enhances the solubilization of *n*-heptane. The addition of KC_{12} at very low concentrations of additive acts somewhat like an electrolyte but at higher concentrations the diluent effects of the shorter chain soap with its lower solubilizing power are seen. Similar initial salt-like effects followed by a decrease in solubilizing power are noted when KC_8 is the additive.

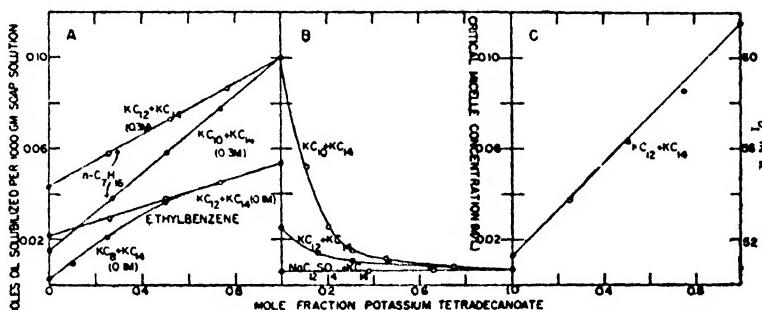


FIG. 13. Changes in (A) solubilization of *n*-heptane and ethylbenzene, (B) critical micelle concentration, and (C) the intermicellar x-ray spacing in various soap mixtures (75, 105, 109, 117, 229).

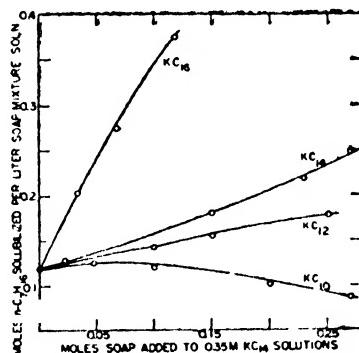


FIG. 14. Solubilization of *n*-heptane in soap mixtures all of which contain 0.35 M potassium tetradecanoate.

McBain and Green (149) have obtained, for the ratio of grams of Orange OT solubilized per mole of soap for 50:50 mixtures of KC_{12} and KC_{14} , constant values which are found to lie between those for the single soaps. Thus at 25°C. these ratios are 1.04 for KC_{12} , 1.92 for KC_{14} , and 1.42 for equimolar mixtures of KC_{12} and KC_{14} . At 50°C. these values were 1.62, 2.95, and 2.18, respectively.

B. Effect of other polar additives

The first investigation of mixed films was the work of Leathes (135, 136), who found that when the proportions were one molecule of lecithin to two or four molecules of myristic or another fatty acid which gives an expanded film, the

effect of the lecithin was to condense the film. The addition of hydrocarbons such as tetradecane to fatty acid films over 0.01 M hydrochloric acid has been shown to have very little effect on force-area curves (177), whereas a stable mixed layer due to molecular interactions in the film is obtained when a soluble substance—and one therefore incapable of giving by itself a stable film—is injected into the substrate on which the normal layer is formed (214). Schulman and Stenhagen (216) have shown the formation in films of complexes of compounds such as cetyl alcohol and sodium cetyl sulfate which in the presence of water cannot be expected to form compounds in the chemical sense of the word. Cockbain and Schulman (23) indicate that there are different modes of interaction according to the nature of the chains and the polar groups. Further, it has been indicated that a liquid-expanded film is made more condensed by addition of a substance which gives a condensed film (139) and the condensing action is found to increase with the length of the hydrocarbon chain (71). Also, an alcohol condenses an acid more than the corresponding acid, and an amine additive is found to show the largest effect. These monolayer effects can be seen to be directly correlatable with changes in solubilization when various polar compounds are used as additives or builders. When alcohols of varying chain length are added to opaque viscous masses of sodium oleate (concentrations > 25 per cent) containing equal amounts of water and benzene, these systems become transparent (212), indicating that this involves an enhancement of solubilization according to the interpretation which will be discussed below (114). According to conductivity measurements, up to amyl alcohol the transparent systems have water as the continuous phase, *n*-hexyl and longer alcohols are oil-continuous systems. In contrast, marked increases in resistance of some 3 to 4 decades are observed in similar systems, in which undecane-3 sodium sulfate (255a) and Aerosol AY and Aerosol MA (118) are the solubilizers, when increasing amounts of various long-chain alcohols are used as additives. Branching in the alcohol chain, probably a function of steric effects in adlineation between the two molecules (91), results in the use of about 2.5 times more 2-ethyl-1-hexanol than 1-hexanol to arrive at transparent fluid systems. It has been proposed by Schulman and co-workers that x-ray and light-scattering measurements (210, 213, 215) on these systems should throw some light on the gap between swollen micelles (solubilization) and emulsion droplets (emulsification). However, it must be emphasized that solubilization must be considered to be a thermodynamically stable solution, i.e., a single phase, whereas emulsification involves the formation of two distinct phases. The following discussion must thus be considered solely from the point of view of emulsification. The diameters of the droplets are seen to increase in a regular manner with decrease in potassium oleate concentrations in both the oil- and the water-continuous systems. The data on light-scattering experiments in figure 15 agree with those calculated on the concept of uniform water spheres in oil or uniform oil spheres in water according to the formula:

$$\frac{3 \times \text{volume of dispersed phase}}{\text{area of interfacial monolayer}} = \text{radius of oil or water droplet}$$

It was found that the corrected Bragg x-ray figures for large diameters are greater than those calculated from surface chemical data. All three measurements are in close agreement for diameters less than 300 Å. These authors consider these systems to be structures of short cylinders or short lamellae of soap-alcohol molecules with oil and water between the layers. In similar qualitative measurements, Winsor (254) assumes that the inversions occur from oil to water continuum containing spherical micelles through a series of lamellar micelles. Dervichian and Pillet (38) have shown that complex formation occurs between lecithin and fatty acids. A mixture of 1 mole of lecithin with 2–10 moles of oleic acid spreads over an area about 18 per cent less than the calculated areas for the quantities of components used. Dreger *et al.* (41) have shown that the

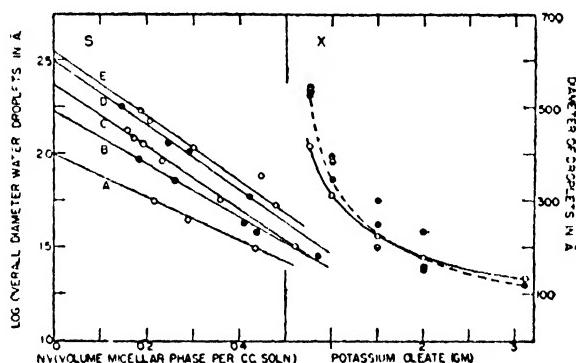


FIG. 15. Light-scattering (S) and x-ray (X) diameters of system potassium oleate 5 ml. water-benzene-cyclohexanol. S: (A) 0.75 ml. oleic acid, (B) 1.00 ml. oleic acid, (C) 1.50 ml. oleic acid, (D) 2.00 ml. oleic acid, (E) 3.16 ml. oleic acid. X: dimensions of corrected x-ray spacings in oil-water systems with varying soap-alcohol concentrations; 5 ml. oil and 5 ml. water. Water droplets: ●, observed; ○, calculated. Oil droplets: ◉, observed; ◇, calculated (210, 215).

detergency of sodium alkyl sulfates diminishes as the sulfate group recedes from the end of the hydrocarbon chain. These results were confirmed by Winsor (253), who showed that sodium stearate readily displaced sodium *n*-tetradecyl sulfate from the surface layer of aqueous solutions and that the more readily displaced surface-active materials (those with poorer detergent properties) were those with the sulfate group farthest from the terminal carbon.

If the evidence as to two loci of solubilization based on film penetration, x-ray, and changes in rate of solubilization data are correct, then it should be possible to show that hydrocarbons and polar compounds are incorporated in micelles independently of each other. The addition of hydrocarbons which swell the center hydrocarbon region of the micelle should make it possible for the micelle containing solubilized hydrocarbon to incorporate more polar compound in its palisade layer. The data in figure 3 show this effect (114), and an explanation based on these assumptions is included at that point. When long-chain alcohols are added to soap solutions, the soap-alcohol micelles that are formed are found

to solubilize as much as eight to ten times the amount of hydrocarbon normally soluble in soap solutions of the same total normality (114). The data in table 14 show the increase in solubilization of *n*-heptane in KC₁₄-1-heptanol micelles and these are compared with the solubilities of *n*-heptane in KC₁₄ solutions. The effect of increasing alcohol chain length on the enhancement of solubilization is shown in figure 16 and the changes in solubilizing power with change in polarity of the additive are indicated in figure 17. A higher degree of order in the alcohol-soap micelles can be advanced from the results on penetration and changes in film pressure (139) for the mixed micelles than for soap micelles, which, however, cannot account for these enhanced solubilizations. The penetration of the alcohol into the soap palisade layer, coupled with a somewhat lower degree of order, would result in the production of a much larger volume capable of solubilizing hydrocarbons. A greater penetration with decrease in polarity COO⁻ > OH > NH₂ > SH would account for the data in figure 17. In the light of the forces involved in micelle formation, there is an increase in total energy of

TABLE 14

Solubilization of n-heptane in solutions of 0.35 M potassium tetradecanovate plus polar additive

MOLES OF ADDITIVE PER 1000 G. KC ₁₄ SOLUTION	MOLES OF <i>n</i> -C ₇ H ₁₆ SOLUBLE PER 1000 G. KC ₁₄ + KC ₁₄ SOLUTION	MOLES OF <i>n</i> -C ₇ H ₁₆ SOLUBLE PER 1000 G. KC ₁₄ + <i>n</i> -C ₇ OH SOLUTION	SOLUBILITY IN KC ₁₄ + ALCOHOL SOLUBILITY IN KC ₁₄ + KC ₁₄
0	0.116	0.116	1.0
0.0411	0.126	0.174	1.38
0.0812	0.142	0.222	1.56
0.120	0.160	0.268	1.67
0.195	0.200	0.356	1.78
0.230	0.217	0.395	1.82
0.270	0.245	0.442	1.81
0.318		0.500	

attraction upon the addition of alcohol molecules to the soap micelle without a corresponding increase in the forces of repulsion, those due to the charged colloidal electrolyte heads. The increase in alcohol chain length and changes in polarity of the amphipathic additive would result in a larger contribution per carbon atom to the energy of attraction, a lower degree of order, and thus to an enhancement of solubilizing power. On the basis of the above hypothesis, the increase in solubilization of Orange OT by KC₁₂ to which was initially added small amounts of benzene, toluene, or hexane and the corresponding decrease in amount solubilized when 5 per cent alcohol is added (66) can readily be explained. Recently, it has been found that the solubility of hydrocarbons such as *n*-heptane in various fatty acid soaps is increased when equivalent amounts of 1-, 2-, 3-, and 4-octanols are the additives (118), the increase being larger with movement of the hydroxyl group from the 1- to the 4-position.

Palit has found that a mixture of solvents would greatly enhance the solubilization of water by cetyltrimethylammonium bromide when neither pure solvent would be effective (183). Thus in this system, the addition of chloroform

to either benzene or carbon tetrachloride would result in an initial increase in solubilization of water followed by a decrease when the concentration of chloroform was further increased, as is seen in figure 18. If these solubilization data are due to the formation and breakdown of the McBain-Hess lamellar micelle, it is

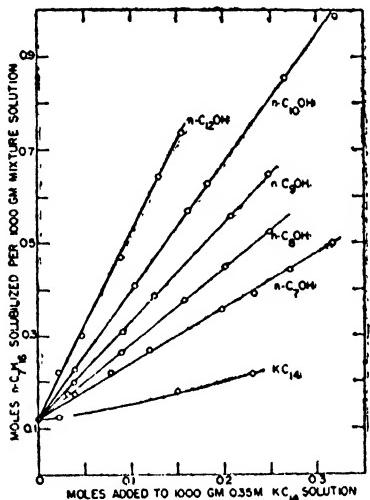


FIG. 16

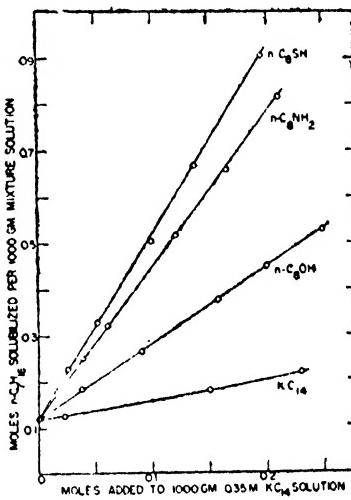


FIG. 17

FIG. 16. Enhancement of solubilization of *n*-heptane in 0.35 M potassium tetradecanoate solutions containing various long-chain alcohols as additives (25°C.).

FIG. 17. Effect of change in polar group of additive upon solubilization of *n*-heptane in 0.35 M potassium tetradecanoate solutions (25°C.).

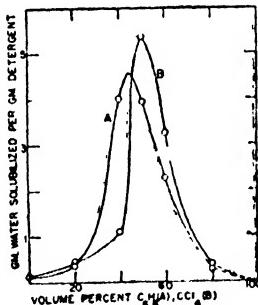


FIG. 18. Solubilization of water in solutions of 1 g. cetyltrimethylammonium bromide in 5 ml. chloroform-additive solvents at 30°C. (183).

difficult to see how these micelles can accommodate about five times their own weight of water in the interlayer spaces without producing a great perceptible heterogeneity. It appears that these results are more readily explainable on the basis of phenomena noted by Winsor (254), in which there is a transition from one micellar form to another, on the results noted by Schulman *et al.* (210, 213, 215) on the marked increase in solubility upon the addition of cyclohexanol, and on

the data reported on eight- to ten-fold increases in the solubilization of *n*-heptane by added long-chain alcohols and amines (112, 114). Further viscometric, optical, and x-ray investigations on all these systems will assist in a final clarification of these phenomena.

Detergent and solubility properties of commercial preparations were enhanced by the addition of fatty acid amides of an alkylolamine (156) and of lauryl alcohol to naphthalenesulfonates (159). The addition of 0.1–20 per cent by weight of an organic builder such as the lower monohydric alcohols or the glycol esters of higher fatty acids to alkyl sulfates or sulfonates produces a detergent composition with improved stable foams (254). Various other organic builders and mixtures, as well as mixtures of surface-active agents with each other, have been mentioned by Schwartz and Perry (217), particularly with regard to the patent literature.

TABLE 15

Figures indicate mole ratio of builder to hardness required for effective soap protection at 57°C. (174)

	Na ₂ PO ₄	Na ₂ O· 3SiO ₂	Na ₂ CO ₃				
	QUADRAFOS	POLYFOS	CALGON	TSP	TSP		
Oleate	1	1	1	1	5	4	>5
Laurate	1	1	1	2	5	>5	>5
Ricinoleate	1	2	2	3	>5	5	>5
Myristate	2	2	1	3	>5	>5	>5
Elaidate	2	2	2	4	>5	5	>5
Palmitate	2	3	3	>5	>5	5	>5

C. Electrolytes as additives

The effect of added electrolytes on the solubility of calcium and magnesium soaps in the sodium soaps, using a foam stability test (172), shows that a minimum mole ratio of builder to calcium or magnesium salts is required to prevent the formation of alkaline earth soaps (174). The mole ratios, as seen in table 15, vary for each soap studied and with the particular calcium or magnesium salt and builder combinations. However for a particular soap, it is seen that a smaller amount of builder with increased charge is necessary for effective soap protection. The effect of added electrolyte on the solubilization of hydrocarbons is found to proceed in the same way, but the opposite effect is noted when polar compounds are solubilized in the presence of electrolytes (115). However, a transition occurs as the length of the polar compound is increased so that the effects noted in table 15 may be explained on this basis. The addition of sodium chloride and lithium chloride is found to decrease the rate of solution of KC₁₆, whereas potassium chloride increases this rate (220).

The brief discussion in the introduction to the section on additives mentioned the presence of a considerable technical and patent literature involving the use of electrolytes as additives for various commercial preparations. Since it is not possible to cover this application completely, no attempt will be made here to do so, since no information may be obtained from these systems as to struc-

tural effects coupled with electrolyte addition on solubilization. Rather, those data which involve the effect of electrolytes on well-characterized soaps and detergents will be discussed particularly from the point of view of information regarding loci of solubilization which might be obtained from them. However, it is worth noting that, in a recent review, Harris (76) has indicated that the addition of ionic electrolytes to anionic surface-active agents can bring about the following changes: reduce surface and interfacial tension, reduce critical conductivity, improve wetting speed, increase lather, and increase detergency. The addition of anionic electrolytes (silicates, phosphates, etc.) to cationic surface-active agents in general results in inactivation of the detergent. The addition of cationic electrolytes (calcium and aluminum chloride) in general exhibits only a slight effect. Addition of ionic electrolytes to a nonionic surface-active agent results in essentially no effect upon wetting. The valence of the added anionic or cationic builder has a marked effect upon the physicochemical properties of anionic surface-active agents. Markedly smaller amounts of polyvalent anionic or cationic builders are required to produce a given change in property. Excessive amounts beyond the optimum generally result in significant reduction in surface activity. Builders for anionic surface-active agents which hydrolyze to yield alkaline or acid solutions are better builders than those which provide essentially neutral solutions. Builder addition to anionic agents can result in a two- to ten-fold decrease in the amount of surface-active agent necessary to produce a given result.

Hartley (80) studied the effect of added sodium chloride on the solubilization of azobenzene in cetylpyridinium chloride. The most complete data in this study cover the low concentration range of detergent, as seen in figure 19. A plot of these data in this manner, in contrast to the manner in which the author treated his data, allows one to determine the C.M.C. of these systems from the intersection of the two lines which show the solubility changes. The insert in figure 19 indicates the change in C.M.C. with added sodium chloride as obtained from these intercepts. Many similar studies have been made (4, 66, 80, 115, 126, 149, 152, 155, 161, 162, 163, 169, 229). Thus McBain and Johnson found similar effects when potassium chloride was added to KC_{12} and KC_{14} (152) and McBain and Green (149) extended these studies to wider concentrations of KC_{12} in 1.0 *N* concentrations of different salts. For the solubilization of Orange OT in KC_{12} , $KOH > KCNS > KCl = K_2SO_4 >$ no salt when added in equimolar concentrations (149). However, it was found for the solubilization of ethylbenzene (229) in KC_{14} that $NaCl > KCl > K_2SO_4 > K_4Fe(CN)_6 \cdot 3H_2O$ when added in equivalent amounts, a result which does not agree with the work of the previous authors. Also, in the solubilization of *n*-heptane the increase in solubilization is seen in figure 20 to follow the same order: $KCl > K_2SO_4 > K_4Fe(CN)_6 \cdot 3H_2O$. It should be repeated here that these salts in equivalent amounts have been found to result in an equal depression of the C.M.C. (27, 109). No data are available which would indicate whether changes in solubilization in the region of the C.M.C., as is seen in figure 19 (80), would occur when equivalent amounts of various electrolytes are used as additives.

Recently, differences in the effect of added salts on the solubilization of

various compounds have been noted (115, 126, 204). The addition of sodium chloride or potassium chloride to 0.1 *N* cetylpyridinium chloride (C.M.C. = 0.0009 *N* in salt-free systems) will result in an initial increase in the solubilization of benzene followed by a decrease at about 0.5 *N* salt concentration and an increase for *n*-octane up to about 1.0 *N* salt (204). However, when 1-octanol is solubilized a decrease is noted upon the addition of electrolyte. Similar results are reported to occur in dilute (0.0125 *N*) solutions. When compared to the C.M.C. values of cetylpyridinium chloride in the presence of added salt (about

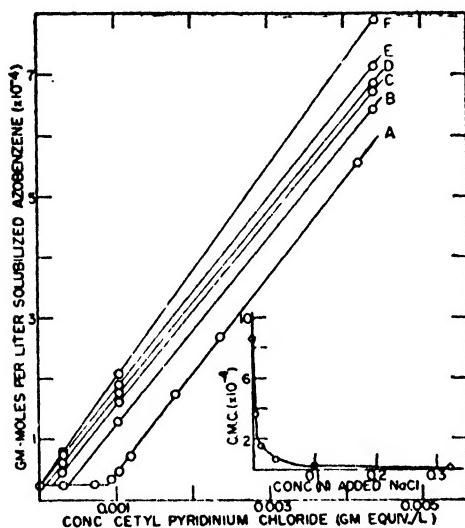


FIG. 19

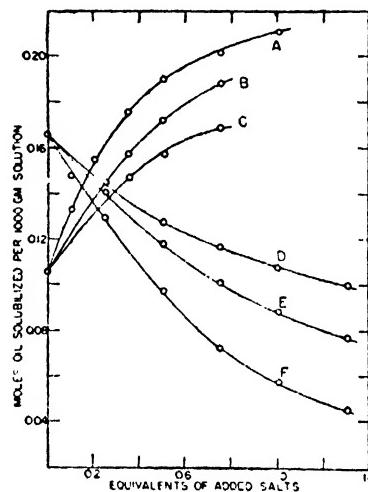


FIG. 20

Fig. 19. Effect of added sodium chloride on solubilization of azobenzene in cetylpyridinium chloride at 25°C.: (A) 0, (B) 0.0032 *N*, (C) 0.01 *N*, (D) 0.032 *N*, (E) 0.1 *N*, (F) 0.32 *N* sodium chloride. Insert shows the effect of added sodium chloride on critical micelle concentration as obtained from the solubilization of azobenzene (80).

Fig. 20. Effect of addition of various electrolytes on solubilization of *n*-heptane in 0.32 *M* KC_{14} : (A) potassium chloride, (B) potassium sulfate, (C) potassium ferrocyanide. Effect of addition of various electrolytes on solubilization of 1-octanol in 0.32 *M* KC_{14} : (D) potassium ferrocyanide, (E) potassium sulfate, (F) potassium chloride.

0.0001–0.0003 *N*, as seen in the insert in figure 19) this concentration is seen to be about 100 times the C.M.C., and thus micelles with maximum colloid properties may have been formed at this concentration. These authors suggest that with this polar compound, the solubilization occurs on or between the polar ends of the micelles that are exposed to the water. Further, they believe that the added salt is in competition with the solubilized material at the polar ends of the detergent molecules and interferes with its solubilization. They use the evidence of Tartar and Cadle (233), which indicates that salts are sorbed by the micelles.

A careful investigation of the solubilization data of various dyes in fatty

acid soaps and in dodecylamine hydrochloride in the presence of added salts (126) shows cross-overs in plots of amount of dye solubilized in the presence and absence of salts. Thus, at about 0.045 M KC₁₂ there is a transition in the amount of dimethylaminoazobenzene (DMAB) solubilized in the presence of added potassium chloride. Below this concentration, DMAB is more soluble in the salt-soap system than in the pure soap; above this concentration the relative solubilities are reversed. This transition occurs at about 0.125 N NaC₁₂ in the presence of 0.1 N sodium chloride, at about 0.112 N KC₁₂ in 1 N potassium chloride, and at about 0.4 N KC₁₀ in the presence of various salts. When other dyes such as *trans*-azobenzene and Orange OT are solubilized in similar systems, no such transitions are found to occur.

These changes in solubilization between polar and nonpolar compounds in the presence of various electrolytes and the data from some experiments which were so planned as to give additional information as to the loci of solubilization

TABLE 16

Solubilization of n-heptane and 1-octanol in 0.05 N potassium tetradecanoate with added potassium chloride

MOLES OF KCl PER 1000 G. OF SOLUTION	SOLUBILITY (S) IN MOLES OF n-C ₇ H ₁₆ PER 1000 G. OF SOLUTION	$\frac{S \text{ } n\text{-C}_7\text{H}_{16} \text{ (ADDED KCl)}}{S \text{ } n\text{-C}_7\text{H}_{16} \text{ (NO KCl)}}$	MOLES OF n-C ₉ OH PER 1000 G. OF SOLUTION	$\frac{S \text{ } n\text{-C}_9\text{OH} \text{ (ADDED KCl)}}{S \text{ } n\text{-C}_9\text{OH} \text{ (NO KCl)}}$
0	0.0087	1.0	0.024	1.0
0.10			0.028	1.16
0.20	0.016	1.84		
0.25			0.032	1.33
0.35	0.019	2.18		
0.50	0.023	2.65	0.036	1.50
0.75			0.029	1.20
1.00	0.030	3.45	0.020	0.83

(115) can best be explained on the hypothesis that at least two of these loci exist in the micelle. If, as has been mentioned previously, one accepts the hypothesis that the energies involved in micelle formation are the forces of repulsion of like-charged heads and the attractive forces, van der Waals in nature, of the long hydrocarbon tails, then any additive which results in an increase or a decrease of either or both of these forces will result in a change in size and/or shape of the micelle and a corresponding change in the volume available for solubilization. It has been shown, in a previous section on polar additives, that an increase in the solubilization of a polar compound will occur when a hydrocarbon is added and that the addition of a polar compound will greatly enhance the solubility of hydrocarbons (114). Thus other additives, such as electrolytes, which result in changes in these repulsive and attractive forces, should show corresponding changes in solubilization. These additives will result in an effective decrease in the energy of repulsion of like-charged soap heads and will thus increase the equilibrium size of the micelle. The added electrolyte will screen

the action of the charges on the micelle and will result in a decrease in the electrical work of repulsion. Debye has shown that there is a linear increase in the molecular weight of the dodecylamine hydrochloride micelle with equivalents of added chloride-ion concentration (32, 33). Thus for the solubilization of hydrocarbons, those which enter the micelle center and result in increases in long x-ray spacings, it is to be expected that there will be an enhancement in solubility upon the addition of electrolytes. Further, since there is this decrease in the energy of repulsion upon the addition of electrolytes, it would follow that there would be a decrease in the effective volume in the soap palisade layer available for solubilization. Thus one would expect a marked decrease in the amount of solubilized long-chain alcohols in the presence of added salts.

The data in figure 20 (115) show the effect of added electrolyte on the solubilization in 0.32 M KC_{14} of both hydrocarbon, *n*-heptane, and polar compound, 1-octanol. The addition of potassium chloride results in an increase in the solubility of *n*-heptane and a corresponding decrease in that of 1-octanol. The added electrolytes which have least effect on the enhancement of solubilization of *n*-heptane are seen to cause the smallest decrease in the solubility of 1-octanol.

Richards and McBain (204) report that at both high (0.1 N) and low (0.012 N) concentrations of cetylpyridinium chloride, the addition of electrolytes results in a decrease in the solubilization of 1-octanol. In contrast to these results it has been found that at 0.007 M KC_{14} , the addition of potassium chloride results in an increase in the solubility of both *n*-heptane and 1-octanol and at 0.32 M KC_{14} plus added salt the solubility of the hydrocarbon increases while that of the polar compound decreases (115). At 0.05 M KC_{14} a transition region for the solubility of 1-octanol is noted. There is an increase up to about 0.5 N potassium chloride, followed by a decrease at higher added salt concentrations. The data covering the transition region are seen in table 16. It is expected that this transition region will shift with change in nature of the electrolyte additive. This transition is probably related to the KC_{14} micelles attaining maximum colloidal properties at this concentration in the presence of 0.5 M potassium chloride.

It is to be expected that, if these transitions occur, similar effects should be noted if the added electrolyte is kept constant while the soap concentration is varied. Thus when *n*-heptane and 1-octanol are solubilized in KC_{14} and in KC_{14} plus 0.25 M potassium chloride, results such as those seen in figure 21 are obtained (115). The cross-overs are similar to those which have been obtained in the solubilization of DMAB (126) in soap-salt and in salt-free solutions but are more striking because of the somewhat higher initial solubility of the 1-octanol. It is probable that the cross-overs noted in the dye solubilization can be accounted for by this mechanism.

Certain anomalies are to be expected in the effect of salts on solubilization of alcohols if the length of the alcohol is increased so that the overall effect of the polar group is diluted as the hydrocarbon portion of the alcohol is increased. This factor is indicated by the data in figure 22, where the solubilities of C_7 , C_9 , C_{10} , and C_{12} alcohols in the presence of increased potassium chloride concentra-

tions show another transition effect. The continued increase in hydrophobic properties as the chain length of the alcohols is increased is quite evident from their solubilization data. It is seen that a marked change occurs between the C_8 and the C_{10} alcohol where KC_{14} is the solubilizer. This might indicate that little or none of the C_8 hydrocarbon tail extends into the hydrocarbon center of the micelle and that a portion of the C_{10} and more of the C_{12} alcohol penetrates into the micelle center and possibly into the adjacent palisade layer. Preliminary results from this laboratory with KC_{12} indicate that the transition occurs with the C_8 alcohol, but additional evidence, now being obtained, will be necessary

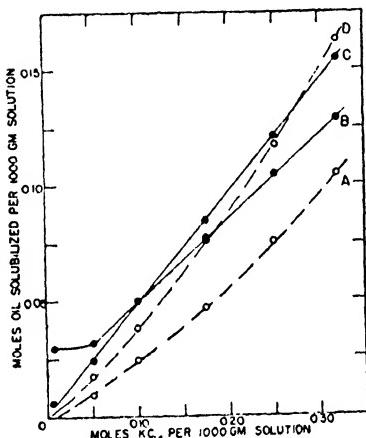


FIG. 21.

FIG. 21. Effect of added potassium chloride upon the solubilization of *n*-heptane and 1-octanol in potassium tetradecanoate solutions at 25°C.: (A) *n*-heptane in KC_{14} , (B) 1-octanol in KC_{14} , (C) 1-octanol in KC_{14} , (D) *n*-heptane in 0.25 M KCl + KC_{14} , (E) 1-octanol in 0.25 M KCl + KC_{14} .

FIG. 22. Effect of chain length of alcohol on solubilization in 0.32 M KC_{14} solution plus added potassium chloride: (A) 1-dodecanol, (B) 1-octanol, (C) 1-heptanol, (D) 1-decanol, (E) *n*-heptane.

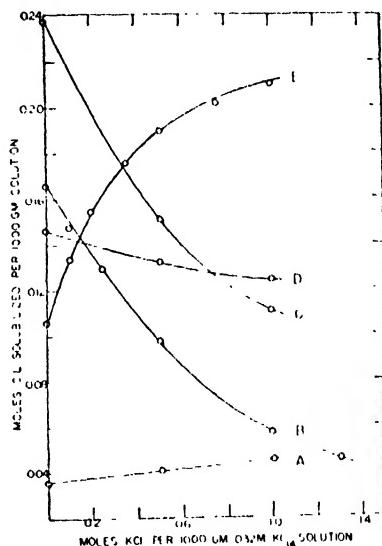


FIG. 22.

before more definite ideas as to the extent of penetration of these long-chain alcohols into the soap micelle can be advanced. The x-ray data showing the changes in both long spacing and in the micellar spacing with increase in alcohol chain length, as seen in figure 12, would indicate some penetration into the micelle center if only the data on the changes in long x-ray spacings were known and if the lamellar theory of micellar form were still predominant. However, it is to be noted that there is a transition occurring between the C_8 and the C_{10} alcohols in these systems in that the D_{h} spacing which is fairly constant between C_4 and C_8 is seen to increase beyond the C_8 alcohol. If the addition of alcohols to soap solutions produces a change from an expanded to a condensed film,

as has been observed in film balance studies (139), then the increases in D_m above C_s can be explained on the basis of swelling within the micelle. Since the two solubilizers, KC_{14} and NaC_{12} sulfate, are of equal chain length and equal C.M.C. values (110), it is to be expected that the transitions which have been noted in solubilization and in x-ray studies should occur with the same alcohol.

The possible free-energy changes involved in the effect of added salts on the solubilization of solids have been discussed qualitatively (255) in the light of the results found by McBain *et al.* (152, 155, 157). If a definite quantity of crystalline hydrocarbon is dissolved in a soap solution, the free energy decrease will be due to a free energy of solution of liquid (or molecularly dispersed) hydrocarbon (as when the oil is initially a liquid) minus the free energy of lattice formation. The total free energy will be less than in the case of the solution of a supercooled liquid oil. For the S_1 systems, the addition of an inorganic salt should at first increase and then decrease the solubility of a solid. For the S_2 systems (polar groups on amphipaths oriented towards each other in the micelle center) it is expected that there will only be a decrease in the solubility of the solid solubilizate upon the addition of an inorganic salt. These effects only partially account for the phenomena observed by McBain *et al.* (152, 155, 157) and by Kolthoff and Stricks (126) working with somewhat similar systems.

IX. STRUCTURE AND ORGANIZATION IN SOAP SOLUTIONS

Solubilization data and x-ray diffraction patterns have been coupled to indicate the presence of different types of associated molecules in soap and detergent solutions. Thus various phenomena such as changes in conductivity, refraction, effect on dye association, freezing point, viscosity, etc. indicate some association at low concentrations, i.e., at the C.M.C. McBain has long postulated the existence of a lamellar, weakly conducting micelle and a small, highly charged, and very highly conducting micelle (144). In contrast to this view Hartley (79) and Lawrence (132) adopted the idea of the spherical micelle originally postulated for soaps by Reyhler (203). The strongest argument in favor of the lamellar micelle was the discovery in 1937 by Hess and Gundermann (88) of the production by transparent soap solutions of an x-ray diffraction pattern of a much more definite nature than that produced by normal liquids. This concept has been accepted until very recently by most investigators, particularly by those using x-ray techniques such as Hess, Kiessig, and their collaborators (88, 89, 101), Krishnamurti (127), Dervichian and Lachampt (37), McBain and his coworkers (144), Harkins *et al.* (72), Hughes, Sawyer, and Vinograd (97), and Stauff (228). The strongest proponent for the spherical micelle during this period was Hartley (79, 84). Winsor (254) postulates the existence of a lamellar micelle if the ratio (R) of the solvent attraction between detergent and oil in the solubilized phase to the solvent attraction between detergent and water (or inorganic salt solution) is equal to 1. The detergent in this ratio is taken to be the amphipathic substance solvated by chemical and van der Waals forces by both oil and water. In this system, there would be no tendency for distortion in the lamellae and the plane would have maximum extension, resulting in gelation. The formation of very viscous, gel-like bire-

fringent systems has been observed in many of the mixtures described above (36, 115, 254, 255). If R were to increase or decrease markedly, it is proposed that there might be a tendency for the planes of the lamellae to curl and to result in spheroidal lipophilic or spheroidal hydrophilic micelles, respectively. Winsor believes in a probable coexistence of these three forms in equilibrium in solution, the configuration present to the greatest extent varying according to the temperature and the composition of the system. In the isotropic systems the configurational changes, the intermicellar equilibrium, are probably much more mobile, and any particular configuration or micelle would have only a transient individual existence (255a). He appears to go to the opposite extreme to that of the x-ray workers, in that he minimizes the importance of organized structure, although he does picture his intermediate anisotropic gel phase (intermediate between systems containing excesses of water or of oil) as being a lamellar intermediate.

McBain believes in the existence of small colloidal particles (smaller than the spherical micelle), as well as spherical and lamellar micelles, since he says that it is impossible for anyone to explain all the properties exhibited by soap solutions or even their x-ray behavior with only one kind of micelle (144a). He states that, "if there is any way in which ions or ion pairs can come together or associate with any reduction in free energy, as by reducing interfacial energy or by more uninterrupted hydrogen bonding of the water, then that complex must exist, however slight, in soap solutions. Each size, shape, and arrangement will form in proportion to the reduction of free energy that it offers under each condition of concentration, temperature, and the presence of other salts and materials."

This concept of polydispersity in soap solutions does not agree too well with the monodispersity of soap and detergent solutions, as determined by the diffusion and ultracentrifugal studies of Hakala (68) and Vetter (244), nor with the concepts as advanced by Debye (32, 33) from calculations resulting from light-scattering measurements on alkylamine hydrochlorides. Hartley (84a), in a discussion of the multiplicity of micelle form as advanced by Winsor, points out that the transition from molecular dispersion to micellar dispersion in a soap solution does approximate in mathematical form to a phase change. It is noted that simple unaggregated soap molecules convert to micelles at a fairly sharply defined critical concentration (C.M.C.), and it is to be expected that the change from one type of micelle to another would have a similarly critical transition point. This concept finds added support in the sharpness of the range in which the resistance changes very markedly, owing to micelle inversion brought about by small changes in temperature or in the concentration of electrolytes or long-chain alcohols (118, 255a).

Stauff (228) found in curd fibers of NaC_{14} sulfate two rings due to short spacings at 20°C. and one in a clear solution of this system at 70°C. These values were 4.55, 4.00, and 4.60 Å., respectively. These values fused together in solution to 4.60 Å. and were found to be constant with concentration, whereas the bands due to long spacings were found to decrease with increase in concentration.

A major point emphasized by the proponents of the lamellar micelle was

the fact that one had to have a certain degree of order or orientation to obtain x-ray patterns of the type found for soap solutions and that spherical micelles could not produce an x-ray pattern. Thus when Mattoon, Stearns, and Harkins (142) first found x-ray evidence for the presence of a two-layer micelle from a more thorough investigation of the x-ray diffraction photographs, the concept of the idealized lamellar micelle was carried over to promote the idea of a cylindrical micelle (70). These cylindrical micelles were conceived of as being small, nonspherical, and of a thickness equal to double the length of the soap molecule, as being capable of becoming thicker in the presence of added hydrocarbon but not with added alcohols, and as increasing in diameter with added electrolyte; it was also believed that the number of soap molecules would increase with added oils. However, at a second critical concentration, above 7 per cent in the case of KC_{14} , there would be restricted motion of these soap cylinders and the long x-ray intermicellar band would appear. Because this model would present a hydrocarbon interface on a large portion of its surface, it has very recently been changed again by Harkins to one of a quasi-oblate spheroid (74), which is taken as a cross between a cylindrical micelle and an oblate spheroid. An oblate spheroid micelle was presented some time previously (108) on the basis of the interpretation of x-ray and solubilization data then available. From changes in C.M.C. with chain length, it was possible to obtain calculated molecular weights of micelles, using the oblate spheroid as a model (110), which were found to be in good agreement with those determined by light scattering by Debye (32). Corrin has briefly discussed the x-ray diffraction evidence and the idea of a spherical micelle and finds the two not incompatible (25). He dismisses the cylindrical micelle, which has been characterized by Bragg law "spacings," and finds that "the observed x-ray diffraction patterns can arise from a system of spherical micelles and that the Bragg law 'spacings' may be meaningless." In an effort to reconcile the points of view of McBain and of Hartley, Stauff has postulated the existence of at least two types of micelles in soap solutions. Dervichian (35) shows that all the properties of these solutions can be accounted for on the basis of a single type of micelle. The results of x-ray analysis are interpreted by assuming that water molecules are sandwiched between layers composed of elementary micelles of soap. These micelles can also form microcrystalline fibers, in which form they constitute the coagulated gel (coagel) and account for the phenomena observed below the Krafft point. The manner in which layers, ribbons, and fibers can be produced by aggregation of the micelles is discussed (35).

A further point which appears to negate the necessity for the existence of the lamellar micelle is the problem of accounting for the volume changes when hydrocarbons are solubilized. If the added hydrocarbon occupies a non-water layer, between the terminal methyl groups (73, 89), the increase in spacing is much more than would be expected from its inclusion in this location. It has been proposed that there is some secondary effect, by an unknown mechanism, on the water layer (73), or that some of the hydrocarbon penetrates into the soap layers (97).

There would appear to be no mechanism which would limit the size of the

lamellar micelle. The formation of spherical or oblate spheroid micelles (minor axis = two times the length of the soap molecule) can be shown to have limits in size in various environments. The formation of these micelles is controlled by a balance between the work necessary to bring the charged heads together and that gained when the hydrocarbon tails leave the water and come in contact with each other and is in accordance with the thermodynamic principle that the gain in free energy associated with micelle formation can be calculated from the critical concentration. A definite micelle size has been found by Debye (32) by light scattering, by Hartley and Runnicles (85) by diffusion measurements, by Miller and Andersson (175) by ultracentrifuge and diffusion measurements, and by Hakala (68) and Vetter (244) by density, viscosity, and diffusion experiments. The addition of electrolytes will result in a decrease in repulsive energy of the charged heads of the soap molecules, in a decrease in the effective area occupied per head, the curvature of the micelle will decrease, and the equilibrium micelle will increase in size but again will have a limit as does the salt-free micelle. This is in agreement with the experimental increase in micellar size with added electrolyte (32). The changes associated with the addition of other materials—long-chain alcohols, hydrocarbons, and other soaps—can also be explained on this basis. This reasoning has been applied (*vide supra*) to explain the effect of added electrolyte on the increase in solubilization of hydrocarbons and the decrease in the amount of polar compounds solubilized (115).

In a discussion of the laminar micelle theory, particularly in reference to a paper by Dervichian (36), Bernal (12) indicated that the increase in spacing between alternate ionic planes could account for only a fraction of the total water present if the increase is taken to be due to the entry of water between adjacent planes. To take as an example the data of Stauff (228), it is seen that for a C₁₄ sodium sulfate system, the long spacing has increased from its water-free value of 38 Å. to 48 Å. upon the addition of 40 per cent water. The lamellar hypothesis would account for only 40 per cent of the added water; the other 60 per cent of the added water would have to be in contact with the exposed hydrocarbon chains in the lamellar bundles.

If any two-layer micelle structure is accepted, oblate spheroid, quasi-oblate spheroid, sphere, or prolate spheroid, and if an average value of the number of molecules per micelle is taken to be 50-75, then, since there can be no appreciable amount of hydrocarbon surface exposed to the surrounding water medium, it can be seen that the effective area occupied by the charged soap head must be between 60 and 70 Å.² (110). This is in agreement with the value of about 8.5 Å. calculated by Hartley (84) as the minimum mean distance apart, center to center, of the charged ionic heads. This is, of course, much larger than the value of 3 Å. for the radius or 28 Å.² for the area which have been used for the values as calculated from the x-ray data on the basis of the idea of a lamellar micelle (72, 228). The outer diffraction band, 4.6 Å., reported first by Stauff (228) and by others (72, 97), must be due to the somewhat regular orientation of that portion of the hydrocarbon tails of the soap molecules some distance removed (at least 5 Å.) from the charged ionic heads.

Hartley (83) has suggested that a distortion of the spherical micelles present

at low soap concentrations might occur as the soap concentration increases, which would bring the shape of his micelle more in line with the one proposed by the author (110). It has been shown (*vide supra*) that there is a decrease in solubilization of 1-heptanol and an increase of *n*-heptane as electrolyte is added to these systems (115). This would correspond to an increase in micellar size due to the addition of an electrolyte (32), resulting in more volume available for hydrocarbon in the micelle center and less for the polar compound in the palisade layer. Further, it is seen in figure 6 that the rate of solubilization increases for hydrocarbons and decreases for polar compounds as the concentration of soap is increased. The presence of ionic charges around one micelle might be expected to have an influence on those of its neighboring micelles and, as the concentration of soap is increased, this effect would be enhanced. Thus the addition of more soap to a soap solution would result in an increase not only in micellar number but also in micellar size and would account for the different rates of solubilization for polar and nonpolar solubilizates.

In a recent contribution (84) it has been suggested that in concentrated solutions the strong repulsive charges between neighboring micelles will tend to orient these micelles in a regular fashion such that each is at a maximum distance from its nearest neighbors. This order might involve a second critical concentration at which the appearance of the intermicellar x-ray bands first are noticed. This type of close-packed assembly leads to the simple relationship

$$l = r(8\pi/3\phi\sqrt{2})^{1/3}$$

where l = distance between centers of neighboring spheres,

r = radius of the spheres, and

ϕ = fraction of the volume occupied by the spheres.

Calculations based on this structure can account for the changes in l with both added water and added hydrocarbon.

A similar approach was used in calculating the changes occurring in micelle diameter with added hydrocarbon (110). If it is assumed that a soap molecule in the micelle occupies an effective volume corresponding to a truncated cone (effective diameter of charged end about 9.5 Å., corresponding to the closest approach of charged ionic heads of soap molecules on the micelle surface; the hydrocarbon tail has an effective diameter, center to center, of about 5.0 Å.), each cone or soap molecule is found to occupy an effective volume of 630 Å.³ It is possible to determine that an oblate spheroid, with minor axis equal to two times the length of the soap molecule (about 29 Å. for potassium tetradecanoate) and major axis about 61 Å., which can be calculated from the dimensions of the truncated cone, would have a volume of about 45,000 Å.³ This would correspond to a micelle of 78 soap molecules, a value which is in agreement with other values for soaps of this length (32). The hydrocarbon-swollen model would approximate a sphere with radius equivalent to that of the major axis of the spheroid, and the volume available for solubilization would be the internal "free" volume of this expanded micelle. On this basis, there would be approximately 12,000

\AA.^3 per micelle available for a hydrocarbon such as *n*-heptane. At 0.5 N KC_4 , there would be 2.7×10^{21} swollen micelles, which are seen to solubilize about 17.0 g. *n*-heptane per 100 g. solution (see figure 6). This corresponds to about 11,000 \AA.^3 of *n*-heptane per swollen micelle as compared with a value of 12,000 \AA.^3 based on the geometry of an oblate spheroid micelle. The agreement for *n*-heptane and similar hydrocarbons is good, but this reasoning does not carry over too well when similar calculations are made for ethylbenzene (volume of ethylbenzene solubilized = 19,000 \AA.^3 per micelle), which appears to swell the micelle to about the same extent as does *n*-heptane. The change in micellar spacing, D_M , with added hydrocarbon, of 0.30 M sodium dodecyl sulfate is 11.2 \AA. and 11.4 \AA. for ethylbenzene and *n*-heptane, respectively (75). The much larger solubilizing power of the alkylamine hydrochlorides as compared with fatty acid soaps or alkyl sulfates of equal chain length can best be explained by accepting the fact that there is much less order in these former micelles and that the effective area per detergent molecule head is smaller in the amine hydrochlorides than in the other soaps. Film balance studies in which the compression of alcohol or amine films is studied as a function of added soaps and amine hydrochlorides will add much to a clearer understanding of these differences.

This model accounts for part of the solubilization data on hydrocarbons which are available but cannot explain the solubilities of the relatively insoluble polycyclic hydrocarbons. As can be seen in table 10, these compounds require micelles containing up to 6000 molecules. Further, the formation of viscous systems even at relatively low concentrations, as upon the addition of salts and/or polar additives (36, 38, 81, 115, 212, 255), would require some explanation. It is possible that these oblate spheroids may have a large major axis as compared to the minor axis in the presence of added salts, for then the effective area of the charged head will decrease and will approach the area occupied by the hydrocarbon tail as a limit.

The problem of the presence in isotropic soap solutions of more than one type of micelle, of more than one size and/or shape, is still not answerable. It would appear that a carry-over from the crystalline state, in which a certain degree of order is found (lamellar like), to liquid solutions is not at all necessary. The presence of a small, two-layered, spherical or oblate spheroid (ionic micelle of McBain) seems to be universally accepted. Winsor (254), in discussing certain hydrotropic phenomena, talks about the energy differences between three types of micelles being small and believes that they can coexist in equilibrium with each other in various systems. In discussing the solubilization of various dyes, Kolthoff and Stricks (126) believe that two different types of micelles with different solubilizing power occur and that with increasing soap concentration more of the micelles with the greater solubilizing power are formed. This may be explained, however, as was done above, as a type of salt effect in which the ions of one micelle influence those of its closest neighbors. McBain and coworkers (151, 154) state that soap solutions contain different proportions of various micelles in different concentrations. They consider that not only are small two-

layered micelles and lamellar micelles present but that other forms may be expected to be in equilibrium with these. They use x-ray evidence to indicate the presence of the first two forms and various changes that they have observed in studies on solubilization to explain the other nonspecified forms. However, since it has been indicated above that the presence of various additives has a marked influence on the solubilizing power of a soap or detergent, the solubilization evidence advanced to show the existence of other micellar forms can not be readily accepted. Thus Kolthoff and Stricks (126) have shown anomalous breaks in their plots of milligrams of dye solubilized as a function of detergent concentration when potassium nitrate is the additive as well as in other cases. It is known that there is a definite mode of interaction between polycyclics and even between polycyclics and linear molecules containing substituted groups which give to the molecule at a particular point a certain electronic character which is necessary for bonding (22, 120, 249, 250). Further examples of this type of interaction are the starch-iodine and starch-fatty acid complexes which have been explained by Rundle (207, 208) on the basis of a helical arrangement of starch molecules. The polyvinyl alcohol-iodine complexes are blue only under certain definite conditions, but a variation of the structure of the alcohol in part to polyvinyl borate extends considerably the range of conditions in which this latter compound will show blue colors with iodine (251). Thus the complex solubilization patterns exhibited by a number of commercial preparations of detergents (144, 151) some of which contain one or more cyclic or polar groups and probably some electrolyte or other additive could also be explained on the basis of molecular interaction or on the presence of various additives.

Dervichian and Lachampt (37) have reviewed the various possible structures which might be present in soap solutions over the whole concentration range, particularly with reference to the changes which occur at various transition regions, i.e., from molecular dispersion to micellar solution, through the second transition which is indicated by the intermicellar x-ray spacing, and through the Kraft point to water-free systems. They indicate that, upon gelation, the vapor pressure, conductivity, osmotic coefficient, and optical transparency, in contrast to other systems, are preserved in soap solutions. They suggest that gelation involves association or crystallization of the two-layer systems in two directions, however with one favored over the other. This is in contrast to the growth of the lamellar type of micelle in all directions which was postulated by Thiessen and Spychalski (238).

Optical anisotropy as measured by streaming birefringence has not been applied to the determination of macroorientation, such as the presence of lamellae, in soap solutions. It is possible, of course, that the application of high shearing forces necessary for these measurements would tend to break these hypothetical structures apart, since the forces binding adjacent double layers would have to be extremely weak especially when these layers are separated by a water layer of about 40 Å., as in 10 per cent sodium oleate solutions. However, it is known that, in the presence of nonsolubilized polar additives over narrow concentration ranges, these systems appear double refracting. Upon the addition

of high concentrations of salt, just before coagulation, as would be expected, soap solutions show streaming birefringence (148). By means of polarizing microscopy, Thiele (236, 237) has indicated the presence of five forms of associated molecules in aged, but otherwise nonspecified, sodium oleate. These forms are, in order of complexity: (1) hydrophilic soap fibril composed of double layers of soap molecules, (2) a radial sphere made up of clusters of short fibrils, (3) a tactoid-like structure of associated fibrils, (4) a long soap fibril found in hydrophilic sols, and (5) a form of leaflet or plate which appears in hydrophobic sols.

Ralston (197) believes that the concept of the ionic or spherical micelle structure is open to the criticism that an excessive degree of hydration would be encountered, because of the fact that the chains are separated much further as they approach the surface of the sphere. He adds, however, that the internal structure of the micelle would be antagonistic to a high degree of hydration, since it is composed of hydrocarbon chains. This criticism has also been raised by Meyer and van der Wyk (170) and has been answered adequately by Hartley (82). It is worth noting here that Ralston (197) and McBain (144) believe that there are small ionic micelles present below the C.M.C. and that the changes observed at this concentration must be attributable to a solubility effect and not to a spontaneous formation of ionic micelles. Hartley (79) and Tartar (234, 256), on the basis of extensive conductivity studies of the alkanesulfonates, do not accept this premise for, in their opinion, there is no or very little association of the type which results in micelle formation below the C.M.C.

X. APPLICATIONS OF SOLUBILIZATION

The application of solubilization to problems of detergency has been reviewed (2, 21, 30, 63, 144, 224, 239) and nothing can be gained by repetition. The phenomenon of solubilization and the role of soap and detergents in textile processing have been reviewed by Creely (29) and the application of this to various factors in the textile field such as wool scouring, efficiency of grease recovery, and dry-cleaning soaps has been described. However, various biological aspects of emulsification and of solubilization are now becoming more fully understood and a number of applications of these phenomena should be mentioned. It is not planned to be all-inclusive here with regards to this subject, but a number of problems in which solubilization plays a role will be discussed. Those aspects of emulsion polymerization which involve solubilization also will be reviewed briefly. These few applications will serve to indicate the importance of the role of solubilization as applied to biochemical as well as to chemical and industrial problems.

A. BIOLOGICAL ASPECTS OF SOLUBILIZATION

The importance of solubilization as applied to biochemical problems cannot be omitted in any discussion of this phenomenon. The action of surface-active agents in biology and medicine has recently been reviewed by Valko (241), and the nature of the bactericidal action of surface-active agents has been reviewed

by Hotchkiss (95). Interaction of proteins and detergents was the subject of a recent article by Putnam (193), and Glassman has discussed the bactericidal aspects of various surface-active agents (62). The utilization in parasitology of surface-active agents, detergents, and emulsifiers has been the subject of a survey by Dufrenoy and Langeron (44). However, by far the major portions of these reviews cover the interactions of surface-active agents, as electrolytes rather than as micelles, with corresponding media. Certain aspects of the role of solubilization in biological systems have been discussed (93, 226) and only more recent aspects of this subject will be mentioned here.

Even in very small concentrations, the high surface activity of bile salts is indicated by their emulsifying and solubilizing power, which is their most obvious function in digestion. The speed of diffusion of various substances through natural and artificial membranes by bile salts is thus of great importance in resorptive processes. The diffusion of Victoria Blue and Congo Red through Chamberlain filters and collodion ultrafilters (24) and of hemoglobin through collodion (17) is accelerated by bile salts, and bilirubin and eosinate, which are retained by collodion membranes, can pass through when solubilized by bile salts (1, 20).

Merrill (168) found that various solubilizers were effective in bringing insoluble substances into solution even though a membrane permeable only to ions separated them. Vinograd (245) showed that solubilized dye does not pass into water, although the detergent does, and that if the water is replaced by a detergent solution the dye will also come through the membrane. The rate of diffusion of detergent through a membrane is not affected by the presence of solubilized dye. However, when a dye in 1 per cent Aerosol OT is allowed to diffuse into 1 per cent Aerosol OT, its rate is about one-sixth that of the detergent into water. These results indicate that detergents can carry insoluble substances through membranes even though these membranes act as molecular sieves. Mukherjee and Banerjee indicate that the transport and sorption of quinine involves its solubilization by bile salts (176). In the feeding of dehydrocholic acid with other fats to normal persons, icterus patients, or those with cholecystitis or tuberculosis, a decrease is noted in the total fat elimination over that without this added bile acid. This is caused by an increase in the absorption of calcium ions in the intestine in the presence of the bile acid, owing to the formation of bile salt-fat solutions (39). Jones *et al.* (99) demonstrated clinically that fat absorption can be aided by the addition of solubilizing agents, and Kellner (100) showed that when a solubilizing agent is administered to rabbits with cholesterol, blood cholesterol levels become two to three times as high as those obtained without the emulsifier. The above two reports merely confirm past observations that lipids and other water-insoluble material are more readily absorbed when solubilizers and emulsifiers are present. Quagliariello and Foscolo (196) have shown that the rate of diffusion through a cellophane membrane of oleic acid dispersed in sodium glycocholate is not increased by the addition of lecithin, cholesterol, or bile to the mixture. Frazer (56) believes that the lipolytic hypothesis of fat absorption, in its present form, fails to explain an increasing

number of observations in this field, and many of the assumptions on which it is based are in need of reconsideration. The partition theory has been advanced as an alternate working hypothesis upon which further investigation of the many outstanding problems of fat absorption might be based.

A difference between physical adsorption on a surface and solubilization or complex formation was recently indicated by Beck and Meier (10), who found that the invert soap, phenoxyethyldimethyldodecylammonium bromide, reacts with the lipoids of erythrocytes while it reacts by adsorption only with yeast cells. This was shown by the parallel action of reaction equilibrium curves of the invert soap and lecithin and the soap and erythrocytes, while there were found two similar adsorption curves for the invert soap on the yeast cells and on Norit.

The germicidal action of various soaps and detergents is the subject of a number of recent reviews (43, 103, 104), particularly since Domagk (40) in 1935 pointed out the high potency of the cationic detergents. Both soaps and various synthetic detergents have been used in mixtures with nonsurface-active germicides such as phenols, chlorine derivatives, heavy-metal ions, etc. Gershensonfeld and coworkers (59, 60, 61) have discussed the effect of various solubilizers on the activity of these germicides. It has recently been established that soap increases rather than hinders the germicidal action of phenols, and a large number of anionic and cationic detergents have been used as solubilizers for various phenols (217). The fatty acid sulfates (90) and sulfonated oils (60) have been used with phenolic germicides, and various cationics, which are germicidal themselves, have been used as solubilizers with various phenols (94). According to Ordal and Deromedi (181) two synthetic detergents, dodecylsulfonate and the dioctyl ester of sodium sulfosuccinate, enhance the germicidal action of some phenolic compounds. Berry and Bean (13) report in a preliminary note that the bactericidal activity of a phenol soluble in potassium tetradecanoate commences at the C.M.C. and is a function of the concentration of phenol in the micelle. The maximum bactericidal activity, as measured by the death time of *B. coli*, is attained when the micelles are fully saturated with phenol. The influence of the solvent properties of the paraffin-chain salt micelle on the bactericidal effect of dissolved phenols has been the subject of a recent extensive review (3). With salts of saturated acids of eight to fourteen carbon atoms, it has been shown that the bactericidal power against *Escherichia typhosa* rises with increasing concentrations of *p*-chloro-*m*-cresol (205).

The precipitation of a series of carbonates and phosphates, sulfides, calcium stearate, and a number of important biological constituents has been prevented by the addition of nucleic acids (180) and of sodium adenosine triphosphate (179) to these systems. Similar properties have been ascribed to the alkali salts of triphosphate and other polyphosphates (55). All these substances which act like solubilizing or hydrotropic agents are of the utmost biochemical importance, and they are subject to degradation and transformation by widely distributed and specific enzymes. The appearance, disappearance, and reappearance of these compounds in the light of their remarkable solubilizing properties

can probably best be explained in the light of the mobilization, transportation, and sedimentation of insoluble substances in tissues and in the soil.

Stotz (232) has followed leads recommended by studies of natural digestive processes and, by the simultaneous addition of sodium cholate and various types of enzymes, has found it possible to separate various components of the heart muscle oxidase system. Bieri and Schultze (14) have taken advantage of the solubilizing power of the commercial detergent, Tween, to disperse molecularly known amounts of the insoluble β -carotene for intramuscular injections into vitamin A-deficient rats. Halpern and Biely (69) report that solubilized vitamin A has a greater biological value than its vegetable oil solution. This observation was confirmed by Popper and Volk (190).

Further extension of the solubilizing or dispersing action of detergents has been applied by Ekwall and Setälä (47) to various polycyclic carcinogenic polycyclics. Concentrations of solubilizates were measured qualitatively by the fluorescence of colloid solutions of these polycyclics. These polycyclics are readily adsorbed when animals are painted with these solutions, and indications of skin tumors are evident. Further experiments along several directions are now in progress, and it will be of interest to see whether carcinogens dispersed in this manner and those dissolved in other solvents behave similarly in subcutaneous and intravenous injections. Competition for available carcinogen (*p*-dimethylaminoazobenzene) has been noted when, in addition to this dye, lauric acid or fatty acids of hydrogenated coconut oil are added to the diet (21). No liver tumors were found in rats fed this diet, while 20 per cent of the rats on a fat-free diet and 80, 33-53, and 87 per cent, respectively, of the rats fed on diets containing corn oil, olive oil, and oleic acids showed the development of hepatomas.

The addition of paraffin-chain salts to proteins, enzymes, viruses, bacteria, etc. cannot be considered solubilization as discussed above but, in a larger definition of this term, may fall into this classification. Many water-soluble proteins react with the soap molecules, usually by attraction of oppositely charged ions. This is supported, in part, by the finding that any reaction of nonionic detergents with proteins does not involve this type of electrostatic binding (241), for the interaction in this case, probably of a van der Waals type, is far less effective than in colloidal electrolyte-protein systems. It is not expected that individual micelles would react as a unit with a single protein molecule, for this would mean that about 65-75 soap molecules (number composing a micelle of a C₁₂ soap) would combine with any protein molecule.

Putnam and Neurath (194) have indicated that reaction between protein and detergent will occur at pH values on both sides of the isoelectric point. The reaction of serum albumin with sodium dodecyl sulfate will occur at a pH below the isoelectric point (where protein and detergent are oppositely charged) with the appearance of a precipitate over the mole ratio range of protein to soap of about 0.01 to 0.02. This would indicate an increase in the hydrophobic nature of this complex due to the presence of the hydrocarbon tails of the detergent at the protein interface and would account for the turbidity through

flocculation. It appears doubtful, as Ralston has proposed, that association between protein and detergent possibly involves the binding of small ionic micelles (198), for the number of dodecyl sulfate ions bound per serum albumin molecule is initially only 52 and the second complex has about 100 ions per protein molecule (195). Similarly, egg albumin will react with 15 and 28 molecules of detergent per protein molecule at the isoelectric point (18). If the initial soap molecules bind with the oppositely charged groups, and if the initial binding sites can be assumed to be symmetrically distributed on the surface of the protein molecule (taken as a prolate spheroid), then the minimum area per bound detergent molecule would be about 325 \AA^2 of protein surface. This would appear to invalidate the concept of interaction with associated detergent molecules, for no association can be considered present at such distances of separation. Addition of further detergent results in a loss of opacity through the formation of another complex (194). This, an example of solubilization in these systems, is probably due to the binding of the hydrocarbon tail of the added detergent with the hydrophobic portion of the soap molecule of the original complex, replacing each detergent hydrophobic tail of the original complex with a hydrophilic group.

Addition of detergent will result in a number of changes when added to protein systems such as denaturation (5), stabilization as by inhibition of coagulation (5), complex formation and precipitation, inactivation of enzymatic properties, etc., all of which have been discussed in a recent review (193). Foster was able to make physicochemical studies of the water-insoluble protein, zein, in aqueous detergent solutions (54). These complexes of zein and detergent, in which the detergent must be considered to be bound by van der Waals forces through its hydrophobic tails with corresponding hydrophobic groups on the protein surface, are similar in properties to the soluble complex mentioned above. The original protein, zein, the material being solubilized, must correspond to the insoluble protein-detergent complex as well as to such other compounds as the insoluble dyes.

The influence of solubilizing power in addition to known alkalinity effects on skin irritation can be inferred from the data of Emery and Edwards (48), in which a maximum effect is noted with NaC_{12} . Sodium soaps of shorter fatty acids do not form micelles at the concentrations used and the longer chain soaps form white suspensions (C_{14}) or white gels (C_{16} , C_{18}). The addition of salts enhances the irritation effect (49). Soap mixtures, in general, showed the expected irritation effects (167). A nonirritating soap is produced by removing from soap-making oils, such as coconut and palm, the low-molecular-weight fatty acids which produce the irritation (42).

B. EMULSION POLYMERIZATION

A tremendous impetus has been given to the problem of solubilization with the advent of the use of surface-active agents in emulsion polymerizations. Large amounts of fatty acid and resin soaps are now used in this application. The present consensus of opinion is that the monomer is solubilized in the

soap micelles and that at least a part of the polymerization actually takes place in the solubilized state, i.e., that the initial loci of polymerization are the soap micelles (58, 87, 92, 257, 258). The rate of polymerization is directly dependent on the concentration of soap, and the number of polymer particles formed, for any one soap, is a linear function of the number of micelles present in the initial system (87). Marvel *et al.* (140) have noted that the presence of impurities in the soap affects the polymerization. In the standard GR-S recipe, the use of standard soap results in an 80 per cent conversion at 50°C. in 4 hr., while the use of potassium oleate and sodium alkanesulfonates results in a 67 per cent conversion and a 6 per cent yield, respectively, under the same experimental conditions. Dunbrook (45) has recently reviewed various factors involved in emulsion polymerization and reports that in the GR-S recipe, fatty acid soaps less than eight carbons in length are not suitable for polymerization and that the rate of polymerization increases with concentration and with the chain length of the soap. Soaps above eighteen carbons in length are too insoluble in water to be effective. The addition of lecithin up to 0.4 per cent and ethanolamine up to 1 per cent of soap does not retard polymerization. Wilson and Pfau (252) report that linoleic and linolenic acid soaps retard the polymerization rate of GR-S, whereas purified oleate, elaidate, stearate, and palmitate give about the same yields. Alkali-isomerized linolenic acid shows no retarding action.

Kolthoff and Harris (122) have shown that changes in molecular weight distribution are possible through control of mercaptan availability by increment addition of mercaptan or by changes in mercaptan solubility by structural modification. The types of solubilization discussed above can be applied to explain the formation and properties of certain polymers prepared with identical formulae except that the modifier, often a long-chain mercaptan, in one case is added initially to the soap-water-persulfate mixture before the addition of monomers, and in the second polymerization is added dissolved in the monomers. Depending on the relative reactivity of the monomers used, quite different molecular weight distributions should be possible.

These results can only be explained on the basis of mercaptan availability, for in one case the mercaptan is a part of a mixed micelle, with the —SH group oriented toward the water-detergent interface, and in the other it is partially solubilized with the monomer, occupying the center portion of the micelle around the hydrocarbon tails of the soap molecules. If the soap micelle is the initial locus of emulsion polymerization, as has been indicated, then the availability of mercaptan, in the first case as part of a mixed soap-mercaptan micelle, and in the second, readily available in the solubilized monomer, will markedly affect the molecular weight distribution of the initially polymerized product.

The pH, which is known to affect the solubilizing power of various emulsifiers, is important in emulsion polymerization. Cationics are most effective in acid media, whereas a slightly alkaline system is found to be most suitable for anionic emulsifiers. Nonionic agents of the polyoxyethylene ether type are claimed to be more effective if the pH is kept below 7 (98).

X-ray diffraction studies by Hughes *et al.* (97) on KC₁₂ solutions were used to interpret some of the mechanisms occurring during polymerization of styrene in soap solutions. In this process, the addition of styrene results in an increase in the long spacing, D_L ; upon polymerization, this spacing decreases almost to its original value. Further addition of styrene results in another increase in D_L , which decreases again upon polymerization. These results, coupled with the finding that the number of polymer particles formed is a linear function of the number of micelles present (87), lend support to the hypothesis that the soap micelles are the most important initial loci of polymerization.

XI. SUMMARY

Solubilization, defined as the spontaneous passage of solute molecules of a substance insoluble in water into a dilute aqueous solution of a soap or detergent in which a thermodynamically stable solution is formed, is distinguished from hydrotropy, blending, and emulsification. However, it must be emphasized that solubilization and hydrotropy and related phenomena are essentially similar solubility processes and that this concept of similarities can much better explain the existing data than the use of minor differences which may be found in these various phenomena. There are various methods for determining the limit of solubilization which are based on structural and optical properties of the compounds being solubilized (solubilizate). Limits may be determined by the formation of emulsion droplets (turbidity) when the solubilizates are liquids and by a spectroscopic method when the solubilizate contains an absorbing chromophore. Other properties, such as change in vapor pressure, change in micellar spacing as determined from x-ray spectra, etc., may also be used.

Three types of solubilization are illustrated and the mechanism involved in each class is discussed in the light of the present concepts of micellar size and shape. These are (1) adsorption by the micelle usually on or near the soap-water interface; (2) incorporation into the hydrocarbon center of the micelle; and (3) penetration into the palisade layer of the micelle. There is only fragmentary evidence to support type 1, which may involve solubilizates which are structurally low-molecular-weight polar-nonpolar compounds such as the phenols. Type 2 involves hydrocarbon solubilization, in which the solute molecules are not oriented with respect to the soap-water interface and possibly not oriented in the hydrocarbon-like micelle center. There is evidence that both micellar, D_M , and intermicellar, D_L , x-ray bands increase with added hydrocarbon up to the solubility limit. The third type involves the solubilization of polar-nonpolar compounds in which the solubilizate molecules are oriented fairly perpendicularly to the water interface with the hydrocarbon portion of the molecule penetrating between the hydrocarbon chains of the soap molecules and lying fairly parallel to them. There is no increase, and in certain cases there is a decrease, in D_M , and the high adhesion energy between long-chain alcohol and water as compared with hydrocarbon and water further supports the concept of orientation in these systems.

Solubilization depends on the nature of the solvent, the chain length and

charge of the solubilizer, the structure of the solubilizate, the temperature, and the presence of various additives. Increase in temperature normally results in an increase in the solubilization of hydrocarbons and an increase in the solubilization of water but there are, however, many exceptions. Lengthening the chain of a solubilizer of one particular homologous series increases solubilization. The cationic detergents, such as dodecylamine hydrochloride, are more powerful solubilizers for hydrocarbons than the corresponding anionics of equal chain length. Polar compounds are solubilized more in electrolyte-free systems than are nonpolar hydrocarbons of similar structure. Increase in the molar volume of the solubilizate results in a decrease in solubilization. The addition of electrolytes will enhance the solubilization of hydrocarbons and will decrease the amount of polar compounds incorporated in the micelles. The addition of long-chain polar compounds will markedly increase the solubilization of hydrocarbons above that of a corresponding amount of added colloidal electrolyte. Hydrocarbon addition will swell micelles and will allow for more penetration of polar compounds into the palisade layers of the micelle. It is to be noted that opposite effects are observed in the solubilization of apolar (hydrocarbons) and highly polar (water or inorganic salt solutions) compounds when various changes (additives, temperature, etc. but not concentration) are made in the solubilizing systems.

The various factors involved in solubilization can best be explained on the basis of an oblate spheroid or spherical micelle. Structure and organization in soap and detergent systems are discussed from the solubilization data presented in this review. The importance of solubilization in biological and chemical processes is reviewed.

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THE DETERMINATION OF BOND DISSOCIATION ENERGIES BY PYROLYTIC METHODS

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I. INTRODUCTION

A. Synopsis

The determination of dissociation energies of various chemical bonds is of fundamental importance for the quantitative treatment of chemical processes. In chemical reactions bonds are broken and formed, and in many reactions both processes occur simultaneously. In consequence the magnitudes of dissociation energies are of prime importance for both chemical kinetics and chemical equilibria.

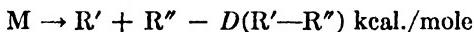
At the outset of this review the definition of the bond dissociation energy is given, which is followed by a brief discussion of the various relationships between this entity and other related quantities: namely, the heat of atomization, the average bond energy, the heat of radical formation, the heat of reaction, and the activation energy of the reaction. This discussion is followed by a short review of various direct methods which may be applied for the estimation of bond dissociation energies.

The main theme of this paper, however, is a critical survey of various pyrolytic methods used for the determination of bond dissociation energies, the examination of principles applied in the interpretation of the experimental material and in computation of the results, and finally a review of the actual results obtained by various workers. This part is divided into two sections, the first dealing with the equilibrium method and the second with the kinetic method.

The paper then concludes with a discussion of some unexplored reactions which might be used for the determination of bond dissociation energies, and with a description of various new methods which might prove useful in this type of work. Tables of bond dissociation energies and heats of formation of various radicals are given in the appendix.

B. The definition of bond dissociation energy

The dissociation energy of the bond A-B in the molecule (or radical) M is the endothermicity of the reaction in which M is decomposed into two fragments R' and R" formed by breaking the bond A-B.¹



It must be stressed that this endothermicity must be computed for the state in which the reactant M and the products R' and R" are in the gaseous phase, at

¹ In cyclic molecules the breaking of certain bonds might lead to the formation of one fragment only.

zero pressure and at 0°K. It follows from the above definition that the dissociation energy of the bond is defined unambiguously by the description of the initial state, i.e., the molecule (or radical) M, and the final state, i.e., the fragments R' and R'', M, R', and R'' being in certain specified electronic states. It is also obvious that no restriction need be imposed on the path of the reaction which leads to this dissociation, since variation of this path does not change the endothermicity of the process.

C. The relationship between the bond dissociation energy and the heat of atomization of a molecule

The rupture of the "first" bond in a polyatomic molecule M requires an expenditure of energy equal to the dissociation energy of the particular bond in the original molecule. As a result of this process new fragments are formed and the breaking of an additional bond requires an amount of work equal to the dissociation energy of this bond referred to the appropriate fragment. The work expended in splitting a further bond is in turn equal to the dissociation energy of this bond in the newly formed fragment. This process is continued stepwise until ultimate atomization of the molecule takes place. Hence, the heat of atomization of the original molecule is equal to the sum of the dissociation energies of all the bonds as they are broken successively until the whole molecule is finally degraded into separate atoms.

This relationship is illustrated by the following two examples:

Example 1



$D(\text{H}-\text{OH}) = D(\text{O}-\text{H})_{\text{in H}_2\text{O}}$ = the dissociation energy of the "first" O—H bond in H_2O

$D(\text{O}-\text{H}) = D(\text{O}-\text{H})_{\text{in OH}}$ = the dissociation energy of the "second" O—H bond in H_2O or the O—H bond dissociation energy in the OH radical

$$Q_a = D(\text{H}-\text{OH}) + D(\text{O}-\text{H})$$

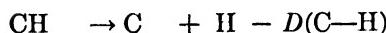
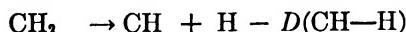
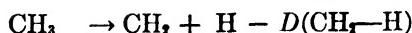
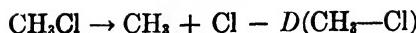
Q_a denotes here the heat of atomization of the original molecule.

It should be emphasized that the dissociation energies of a bond between any two given atoms, but referred to different fragments, will not usually be equal; e.g.:

$$D(\text{O}-\text{H})_{\text{in H}_2\text{O}} = D(\text{H}-\text{OH}) = 118 \text{ kcal./mole}$$

$$D(\text{O}-\text{H})_{\text{in OH}} = D(\text{O}-\text{H}) = 100 \text{ kcal./mole}$$

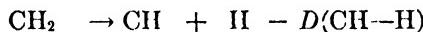
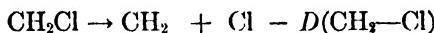
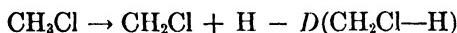
In this particular case, the dissociation energy of the "first" O—H bond is greater than the dissociation energy of the "second" O—H bond in H_2O by 18 kcal./mole.

Example 2

Thus

$$Q_a = D(\text{CH}_3-\text{Cl}) + D(\text{CH}_2-\text{H}) + D(\text{CH}-\text{H}) + D(\text{C}-\text{H})$$

It is permissible, however, to visualize other paths for the atomization process of the methyl chloride molecule, e.g.:



Thus

$$Q_a = D(\text{CH}_2\text{Cl}-\text{H}) + D(\text{CH}_2-\text{Cl}) + D(\text{CH}-\text{H}) + D(\text{C}-\text{H})$$

Both modes of atomization must lead, of course, to the same value for the heat of atomization, although the component dissociation energies need not necessarily be the same; e.g.:

$$D(\text{CH}_3-\text{Cl}) \neq D(\text{CH}_2-\text{Cl})$$

$$D(\text{CH}_2\text{Cl}-\text{H}) \neq D(\text{CH}_2-\text{H})$$

D. The relationship between the bond dissociation energy and the "average bond energy"

The bond dissociation energy is to be distinguished from another quantity which will be referred to in this paper as "average bond energy."² The latter is defined for a molecule of the type AX_n as $1/n$ of its heat of atomization. The absence of a clear definition of the "average bond energy" was recently stressed in a paper by M. G. Evans and M. Szwarc (56). These authors proposed a purely formal and unequivocal definition of the "average bond energy" which can be expressed in nonmathematical language as follows: The "average bond energy" of a bond between two atoms A and B is equal to the work done in separating these two atoms in a process during which all the other bonds are independently and simultaneously extended in such a way that the molecule as a whole swells infinitely whilst preserving its original geometrical form.

² See, for example, L. H. Long and R. G. W. Norrish: Proc. Roy. Soc. (London) **A187**, 337 (1946).

The mathematical representation of the "average bond energy" described in this manner is given, therefore, by the integral

$$\tilde{q}_{a_k} = \int_{r_{k_0}, L}^{\infty} \frac{\partial E}{\partial r_k} \cdot dr_k$$

where E denotes the potential energy of the molecule expressed as a function of all the bond lengths (r_k) and of other required coördinates (α_i), the latter being chosen as the required angles between the bonds; r_{k_0} denotes the value of r_k in the original molecule; L denotes the integration path, which is defined by the following set of equations:

$$\alpha_i = \alpha_{i_0} = \text{const. for all } i$$

$$r_k = \gamma r_{k_0} \quad \text{for all } k$$

γ being a variable which increases from 1 to ∞ . The potential energy E is measured from the zero level represented by the set of separate atoms, each of them being in a specified electronic state.

The following example illustrates the numerical difference between the bond dissociation energy and the "average bond energy."

$$D(\text{H}-\text{OII}) = 118 \text{ kcal./mole}; D(\text{O}-\text{II}) = 100 \text{ kcal./mole}$$

$$\text{"Average bond energy} = 109 \text{ kcal./mole"}$$

i.e., in molecules of the type AX_n the "average bond energy" is the arithmetic mean of all the bond dissociation energies.

The relationship between D and \tilde{q}_a in various molecules of the type AX_n has been discussed more fully in papers by M. Wehrli and G. Milazzo (212) and by H. A. Skinner (161).

E. The relationship between the bond dissociation energy and the heat of formation of radicals

The determination of the dissociation energy of a bond, the rupture of which produces two *identical* radicals (or atoms), enables one to compute the heat of formation of these radicals (or atoms):

$$\Delta H_f \text{ (radical or atom R)} = \frac{1}{2} [\Delta H_f(\text{R}_2) + D(\text{R}-\text{R})]$$

Example 1: The dissociation energy of the $\text{H}-\text{H}$ bond in hydrogen is 104 kcal./mole; hence the heat of formation of hydrogen atoms (from the element in its standard state) is 52 kcal./mole.

$$\Delta H_f(\text{H}) = \frac{1}{2}[D(\text{H}-\text{H})] = \frac{1}{2} \times 104 \text{ kcal./mole}$$

Example 2: The dissociation energy of the $\text{N}-\text{N}$ bond in hydrazine is 60 kcal./mole and the heat of formation of gaseous hydrazine (from the elements in their standard states) is 22 kcal./mole; hence the heat of formation of the NH_2 radical (from the elements in their standard states) is 41 kcal./mole.

$$\begin{aligned}\Delta H_f(\text{NH}_2) &= \frac{1}{2}[\Delta H_f(\text{N}_2\text{H}_4) + D(\text{NH}_2-\text{NH}_2)] \\ &= \frac{1}{2}(22 + 60) \text{ kcal./mole} = 41 \text{ kcal./mole}\end{aligned}$$

If the heats of formation of various radicals or atoms are known it is possible to calculate the related dissociation energies, provided the heats of formation of the required compounds are known. For instance, the heat of formation of gaseous ammonia (from the elements in their standard states) is -11 kcal./mole, and the heats of formation of H atoms and NH₂ radicals have been computed in the examples given above at 52 kcal./mole and 41 kcal./mole, respectively. Thus we can calculate the dissociation energy of the "first" N—H bond in ammonia as follows:

$$\begin{aligned}D(\text{NH}_2-\text{H}) &= \Delta H_f(\text{NH}_2) + \Delta H_f(\text{H}) - \Delta H_f(\text{NH}_3) \\ &= (52 + 41 + 11) \text{ kcal./mole} = 104 \text{ kcal./mole}\end{aligned}$$

The above example illustrates the use of the principle which enables one to derive bond dissociation energies from thermochemical data, provided the heats of formation of the required radicals, or atoms, are known, i.e., if the bond dissociation energies on which these latter quantities are based have been independently determined by some direct methods. It must be stressed that it is by no means possible to compute a bond dissociation energy from purely thermochemical data, without recourse to other bond dissociation energies which have been determined by direct measurements. It is obvious, therefore, that a bond dissociation energy calculated on the basis of thermochemical data and in terms of directly estimated dissociation energies entails the uncertainty and the experimental errors involved in the determination of the latter.³

If the value of the dissociation energy of a bond the rupture of which produces two *different* radicals or atoms is known, then one is able to compute the heat of formation of a radical by reversing the above method. For instance, $D(\text{C}_6\text{H}_5\text{CH}_2-\text{H}) = 77.5$ kcal./mole, the heat of formation of toluene in the gaseous state is 12 kcal./mole, and that of hydrogen atoms is 52 kcal./mole. Thus, the heat of formation of the benzyl radical is found to be 37.5 kcal./mole.

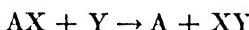
$$\begin{aligned}\Delta H_f(\text{C}_6\text{H}_5\text{CH}_2) &= \Delta H_f(\text{C}_6\text{H}_5\text{CH}_3) + D(\text{C}_6\text{H}_5\text{CH}_2-\text{H}) - \Delta H_f(\text{H}) \\ &= (12 + 77.5 - 52) \text{ kcal./mole} = 37.5 \text{ kcal./mole}\end{aligned}$$

³ For example, the C—F bond dissociation energy in acetyl fluoride was computed by A. S. Carson and H. A. Skinner (37) at 110 kcal./mole. The above authors measured calorimetrically the heat of hydrolysis of acetyl fluoride and their experimental error was ± 0.6 kcal./mole only. The computation of $D(\text{CH}_3\text{CO}-\text{F})$ involves, however, the values of $D(\text{F}-\text{F})$ and $D(\text{CH}_3-\text{CO})$ in addition to their experimental data. These two bond dissociation energies involve considerable uncertainties, owing to the interpretation of experimental data used for their calculation (for example, $D(\text{F}-\text{F})$ has been accepted at 60–65 kcal./mole and at present the new evidence seems to suggest a value of 35–45 kcal./mole) and to experimental errors of measurements. Hence, the uncertainty in $D(\text{CH}_3\text{O}-\text{F})$ is probably of the order of ± 10 kcal./mole, although the experimental error of calorimetric determination of Carson and Skinner is only 0.6 kcal./mole.

It must be emphasized again that this calculation requires a knowledge of both the heat of formation of the second fragment and the dissociation energy.

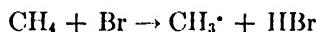
F. The relationship between the bond dissociation energy and the heat of reaction

The heat of reaction is equal to the sum of the dissociation energies of the bonds which are formed minus the sum of the dissociation energies of the bonds which are broken. This relationship is particularly simple for reactions of the type



where Y denotes either an atom or a radical. The heat of this reaction is given as $D(\text{X}-\text{Y}) - D(\text{A}-\text{X})$. Hence, if $D(\text{X}-\text{Y})$ is known, the determination of the heat of reaction will enable one to compute the value of $D(\text{A}-\text{X})$.

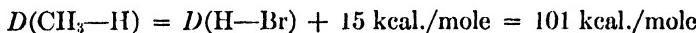
G. B. Kistiakowsky and his collaborators (88) applied this principle in a very ingenious manner to the problem of the estimation of the dissociation energy of the C—H bond in methane. They determined the activation energies of the two reactions



as 18 kcal./mole and 2 kcal./mole, respectively. The difference between these activation energies gave the heat of reaction for



their own recalculation for 0°K. leading to $\Delta H_0^{\circ} = 15$ kcal./mole. On applying the above principle, and taking the $D(\text{H}-\text{Br})$ at 85.8 kcal./mole they concluded:



G. The relationship between the bond dissociation energy and the energy of activation

In most chemical reactions two processes occur simultaneously: the existing bond is broken and a new bond is formed. The activation energy of such a reaction is, of course, a function of the dissociation energies of both the bond which is broken and that which is formed. The relationship between the activation energy and the relevant dissociation energies is, in most instances, of a complex nature. It is not an easy task, therefore, to obtain information concerning the magnitude of the dissociation energies involved in a reaction from a knowledge of the corresponding activation energy of the process.

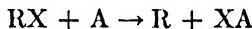
In some cases, however, these relationships are greatly simplified. Firstly, let us consider the unimolecular decomposition of a molecule in which the fission of one bond results in the production of two radicals or atoms. The activation energy of this process will be equal to the dissociation energy of the broken bond if the reverse process, i.e., the recombination of the radicals, corresponds to zero activation energy. Although there are few experimental data available from which we may calculate the activation energy of the recombination process, the evidence

so far accumulated strongly suggests that this activation energy is negligible. There is no theoretical justification whatever to anticipate repulsion forces between two colliding radicals or atoms.⁴ Furthermore, observed spectroscopic data seem to conform closely to potential energy curves which do not show humps. Finally, most reactions between radicals and molecules, if exothermic, seem to have very low activation energies.

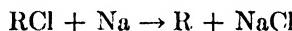
One should notice, however, that the recombination of two triphenylmethyl radicals involves an activation energy of about 7-8 kcal./mole (227). This reaction is an obvious exception, and the calculation by M. Szwarc (184) demonstrates that there are repulsion forces, due to the interaction between the hydrogen atoms of the approaching phenyl groups. These repulsion forces begin to operate when the distance separating the central carbon atoms is still greater than 4 Å., i.e., before the development of any appreciable attraction between these centers.

It seems reasonable, therefore, to make the general assumption that the recombination of radicals or atoms does not involve any activation energy; hence it follows that the activation energy of the discussed dissociation process is equal to the respective bond dissociation energy.

The second case which we shall consider involves a series of reactions of the type:



In each series the radical R is varied, while X and A remain constant. The variation of R changes the bond which is subsequently broken, giving rise to different R—X dissociation energies. On the other hand, it will be noticed that the same bond is formed in every reaction. For such reactions we should expect some systematic increase of the activation energy with the increase of the dissociation energy of the R—X bond. As an example we may quote a series of reactions of the type:

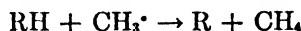


For this series a relationship between the activation energy and the dissociation energy of the R—Cl bond was first proposed by R. A. Ogg, Jr., and M. Polanyi (124) and further developed by M. G. Evans and M. Polanyi (54). It was shown by the above authors that in such a series the increase in activation energy is proportional to the increase in the dissociation energy of the R—Cl bond.

$$\Delta E_a = \alpha \cdot \Delta D$$

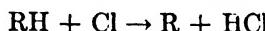
On the basis of theoretical considerations a value of about 0.3 was attributed to α , and the experimental justification of the above relationship was presented in a paper by E. T. Butler and M. Polanyi (35).

Similar relationships have been reported for other series of reactions, e.g.,



⁴ See, however, W. Heitler and G. Rumer (75).

given by H. S. Taylor and J. O. Smith (202), and



given by H. Steiner and H. R. Watson (176).

This type of relationship does not provide information as to the absolute magnitude of the bond dissociation energy; nevertheless it is valuable for the estimation of the gradation in bond dissociation energies. However, the results obtained from this type of investigation cannot be accepted always with complete confidence.

II. THE DIRECT DETERMINATION OF BOND DISSOCIATION ENERGIES

The principles of the evaluation of bond dissociation energies from thermochemical data have already been described in Sections I, E and I, F. In Section II various direct methods applicable to the determination of bond dissociation energies are presented.

A direct estimation of the bond dissociation energy is possible by measuring the amount of energy involved in either the bond-breaking or the bond-forming processes. All the direct methods for estimation of bond dissociation energies can, therefore, be classified into two groups: (A) methods in which the process of bond formation is investigated; (B) methods in which the process of bond rupture is investigated.

It is by no means easy, however, to measure the energy liberated in the bond-formation process. Under ordinary experimental conditions this energy is not liberated in the form of radiation, thus rendering photochemical methods useless. Neither is the energy liberated in bond formation converted into electric energy. The only feasible method, therefore, is to measure the amount of heat liberated in the process of recombination of radicals or atoms. This phenomenon has been known for some time and utilized for various purposes; e.g., the heat liberated in the process of recombination of hydrogen atoms has been used for welding purposes (Langmuir torch) and for measuring the concentration of atoms in a gas stream. This effect was used by F. R. Bichowsky and L. C. Copeland (19) for the estimation of the heat of recombination of hydrogen atoms to hydrogen molecules. The atoms were produced by electric discharge, their concentration was estimated by the effusion method, and the recombination took place on the surface of a calorimeter which was covered by palladium black. The results were satisfactory and $D(\text{H}-\text{H})$ was estimated at 105 ± 3.5 kcal./mole. Similar experiments were repeated with oxygen atoms by L. C. Copeland (43) and by W. H. Rodebush and S. M. Troxel (154). It seems, however, that the method is less reliable in this case. The preliminary report of Copeland suggested a very high value for $D(\text{O}-\text{O})$: namely, 165 ± 5 kcal./mole. The value finally recommended by Copeland and by Rodebush and Troxel of about 131 kcal./mole is still too high (the value accepted at present is 117 kcal./mole) and seems to indicate some inherent defect of the method. The possibility of the participation of metastable oxygen atoms in the recombination was not refuted in a decisive way.

All the other direct estimations hitherto completed have been based on the

bond-splitting process. This method, included in group B, can in turn be divided into three subclasses according to the form in which the energy is supplied for the fission of the bond.

(a) *Photochemical methods*: The energy is supplied in the form of radiation. Under this heading we include the methods based on the investigation of absorption spectra, predissociation phenomena, photodecomposition, photosensitized decomposition, etc.

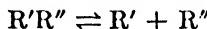
(b) *Electron impact methods*: The energy in this type of investigation is supplied by the kinetic energy of a beam of electrons. This method was used successfully by D. P. Stevenson.

(c) *Thermal or pyrolytic methods*: Here the energy is supplied in the form of thermal energy. These methods are discussed in detail in the following sections. They are described under two main headings: (1) the equilibrium method and (2) the kinetic method. The former deals with those investigations in which equilibrium is attained between the undissociated molecules and the fragments resulting from the fission of the bond in question, and leads to the computation of the heat of dissociation. The latter is based on the kinetics of the bond-breaking process and leads to the determination of the activation energy of the dissociation process. It is shown later that this activation energy might be identified with the bond dissociation energy.

III. DETERMINATION OF BOND DISSOCIATION ENERGIES BY THE EQUILIBRIUM METHOD

A. Principle

The determination of bond dissociation energies by the equilibrium method is based on the measurement of the equilibrium constants of the gaseous reaction:



where R' and R'' denote the radicals or atoms produced by the rupture of the bond in question. These equilibrium constants, estimated at various temperatures, enable us to compute the heat of dissociation by applying the van't Hoff isochore, and the recalculation of the heat of dissociation to zero pressure and 0°K. yields, by definition, the bond dissociation energy.

The experimenter who wishes to determine a bond dissociation energy by the equilibrium method has to consider the problems of: (a) selecting a system in which the required equilibrium may be established and maintained throughout the period necessary for the appropriate measurements to be made; (b) selecting, or devising, a method which will enable him to determine the equilibrium constant with a sufficient degree of accuracy.

The equilibrium method is particularly suitable for estimating the bond dissociation energies of diatomic molecules of the X_2 type. In this case the dissociation process produces the atoms X , and the latter can only recombine into the original molecules X_2 . Such a system, therefore, is very simple and cannot be disturbed by any side reactions.⁵ However, in the case of molecules of the type

⁵ There were speculations about the formation of molecules of the X_3 type. Such a situation is encountered, e.g., in the system O , O_2 , and O_3 at very high temperatures. It was definitely proved, however, that no molecules of the I_3 type exist in the system $I_2 \rightleftharpoons 2I$ (133), and probably no molecules of the Br_3 type disturb the equilibrium $Br_2 \rightleftharpoons 2Br$.

R_2 , R being a radical, the situation is much more complex owing to the occurrence of various secondary processes such as:

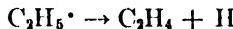
- (a) Reactions between radicals R and molecules R_2 which would lead to products different from RR; e.g., in the hypothetical system $CH_3CH_3 \rightleftharpoons 2CH_3\cdot$ the CH_3 radicals could be removed by the reaction:



- (b) Reactions between two radicals R which would lead to products different from RR; e.g., in the hypothetical system $C_2H_5C_2H_5 \rightleftharpoons 2C_2H_5\cdot$ the radicals $C_2H_5\cdot$ might be removed by a disproportionation:



- (c) Decomposition of radicals R into simpler fragments; e.g., in the hypothetical system $C_2H_5C_2H_5 \rightleftharpoons 2C_2H_5\cdot$ the radicals might decompose according to the equation:



All the side reactions discussed above become more likely at higher temperatures and for longer reaction times, and their participation in the overall process limits the applicability of the equilibrium method; therefore the equilibrium method is particularly suitable for dealing with molecules R_2 , for which the R—R bond is weak, the R radical is inert with respect to R_2 , and thermally very stable, e.g., $N_2O_4 \rightleftharpoons 2NO_2$; $(C_6H_5)_3CC(C_6H_5)_3 \rightleftharpoons 2(C_6H_5)_3C\cdot$.

It is possible, in principle, to calculate the heat of reaction even if the equilibrium constant was measured at one temperature only. These calculations, however, require a knowledge of the partition functions of the molecule $R'R''$ and of the radicals or atoms, R' and R'' . Since partition functions are known accurately only for relatively simple molecules and they are not available for radicals, the method is limited to the estimation of dissociation energies of diatomic molecules.⁶

B. Static manometric method

A known amount of a compound of the type RR is introduced into a reaction vessel of constant volume and heated to a suitable temperature for the time required. After attainment of equilibrium the final pressure is determined. This method yields the average molecular weight, which in conjunction with the known molecular weight of the undisassociated compound RR enables one to deduce the degree of dissociation, α . The equilibrium constant K_\bullet is given by the formula:

$$K_\bullet = \frac{\alpha^2}{1 - \alpha} \cdot P$$

P being the pressure in the system.

In order to achieve sufficient accuracy in measuring the pressure increments,

* For further details see, for example, R. H. Fowler and E. A. Guggenheim: *Statistical Thermodynamics*. Macmillan Company, New York (1940).

the latter must attain some considerable fraction of the total pressure; i.e., it is necessary to choose a temperature range over which the degree of dissociation is adequately large. Table 1, taken from E. W. R. Steacie's monograph (168), gives the temperatures at which a dissociation of 1 per cent is attained for various diatomic molecules at a pressure of 1 mm. of mercury. It is scarcely possible to detect sufficiently accurately the increase of pressure corresponding to 1 per cent of dissociation, and a glance at table 1 shows that a high temperature is required for the determination of bond dissociation energies greater than about 50 kcal./mole. Work at such high temperatures presents many technical difficulties, making the static manometric method very inconvenient.

The difficulties associated with experimentation at high temperatures might be avoided by working at extremely low pressures. This, however, presents new problems, such as the measurement of very low pressures, estimation of minute quantities of material, and, above all, an estimation of the amount of material adsorbed on the walls of the reaction vessel. The latter information is required

TABLE I
Dissociation of diatomic molecules at a pressure of 1 mm. of mercury

COMPOUND	DISSOCIATION ENERGY kcal./mole	T °C.	COMPOUND	DISSOCIATION ENERGY kcal./mole	T °C.
K ₂	11.8	270	Br ₂	45.2	850
Na ₂	17.0	390	Cl ₂	56.9	1040
Li ₂	26.7	590	H ₂	104	1920
I ₂	35.2	680	O ₂	117.4	2000

for estimating the amount of material present in the gas phase, as at very low pressures the amount of adsorbed material may rise to a considerable fraction of the total amount of compound introduced. Obviously, accurate estimation of the adsorbed material would present formidable difficulty.

C. Dissociation energies determined by the static manometric method

(1) I—I bond dissociation energy in the iodine molecule

The first accurate data on the equilibrium $I_2 \rightleftharpoons 2I$ were obtained by G. Starck and M. Bodenstein in 1910 (166). The equilibrium was investigated over a wide temperature range from 800° to 1200°C. The results are self-consistent and the accuracy of the measurements appears to be satisfactory. The heat of dissociation of iodine, recalculated by these authors for 0°K., was estimated at 35.5 kcal./mole.

These investigations were repeated in 1922 by H. Braune and H. Ramstetter (26), and by lowering the total pressure in the reaction vessel to a few millimeters of mercury they succeeded in measuring the equilibria at lower temperatures, i.e., 640–1100°C. The final results, however, seem less satisfactory than those of Starck and Bodenstein, and the value of 35.1 kcal./mole recommended by Braune and Ramstetter is definitely too low.

The most elaborate study of the equilibrium $I_2 \rightleftharpoons 2I$ was undertaken by M. L. Perlman and G. K. Rollefson in 1941 (133). A modern technique was ap-

plied and the experiments were carried out over a temperature range of 450° to 1000°C. Perlman and Rollefson achieved an extremely high degree of accuracy and estimated the dissociation energy of the iodine molecule at 35.514 ± 0.050 kcal./mole. In computing this value a correction was introduced to allow for a deviation of iodine vapor from the perfect gas law. It should be emphasized that the accuracy of this estimation is of the same order as that obtained in the best spectroscopic determinations of $D(I-I)$. The best spectroscopic value, 35.547 ± 0.023 kcal./mole obtained by W. G. Brown (31), agrees excellently with the value 35.514 ± 0.050 kcal./mole recommended by Perlman and Rollefson.

(2) Br—Br bond dissociation energy in the bromine molecule

Values of the dissociation energy of bromine obtained by the static manometric method are much less reliable than those obtained for $D(I-I)$. These studies had to be carried out at temperatures still higher than those required in the study of the iodine system and the investigators were obliged to overcome increasing technical difficulties.

E. P. Parman and G. A. S. Atkinson (131) were the first to show that the apparent molecular weight of bromine vapors varied with temperature, thus indicating the occurrence of the dissociation process. The observed change was, however, too small (80.0 at about 650°C. and 74.3 at about 1050°C.) and their experimental technique too crude to justify any calculations of the heat of the dissociation process.

In 1916 M. Bodenstein and P. Cramer (22) repeated these experiments, using a much more refined technique. Bromine vapor was heated up to 1300°C. in a silica reaction vessel (a platinum reaction vessel was attacked at these temperatures by bromine). Since silica starts to soften at 1300°C., the reaction vessel might be deformed as a result of the differences between the outside and inside pressures. The silica reaction vessel was enclosed therefore in a platinum container, the pressure in the latter being continually adjusted to the pressure in the former. The highest percentage of decomposition observed was 18.3 per cent at 1300°C. and 770 mm. of mercury. The uncorrected value for the Br—Br bond dissociation energy was computed by Bodenstein at 46.5 kcal./mole (compared with the accepted value at present of 45.4 kcal./mole).

The percentage of decomposition of bromine molecule into bromine atoms was estimated experimentally by H. von Wartenberg and F. A. Henglein (211). These authors measured the dissociation at extremely low pressures, of the order of 10^{-3} mm. of mercury, and in consequence could observe the dissociation over a much lower temperature range: namely, 560–730°C. It is interesting to note that the percentage of decomposition computed from Bodenstein and Cramer's equation for $\log K$ agreed closely with that observed directly by von Wartenberg and Henglein.

(3) Cl—Cl bond dissociation energy in the chlorine molecule

The technical difficulties associated with work at extremely high temperatures became serious and manifested themselves in the investigations of the dissociation process $Cl_2 \rightleftharpoons 2Cl$. The early workers were unable to observe any dissoci-

tion, even at temperatures as high as 1200°C. (e.g., see V. Mayer: Ber. **11**, 1426 (1879)). M. Trautz and W. Stäckel (205), who investigated the dissociation of chlorine under atmospheric pressure by heating it in a porcelain reaction vessel up to 1300°C., recorded 1.5 per cent decomposition at 1200°C. and 3 per cent decomposition at 1280°C. They calculated from these data the Cl—Cl bond dissociation energy at 70 kcal./mole, a value which is widely different from that accepted nowadays (57 kcal./mole). Undoubtedly, the degree of dissociation observed by them was too small to render the results accurate enough.

Much better results were obtained by F. A. Henglein (76), who carried out the investigation of the dissociation process of chlorine at pressures of the order of 10^{-3} mm. of mercury. Chlorine was heated in a silica reaction vessel which was enclosed in an evacuated platinum container. This arrangement was required in order to prevent the diffusion of hydrogen into the silica vessel.⁷ The experiments were performed over a temperature range of 700° to 900°C. and the pressure was measured by the Haber-Kerschbaum fiber manometer. The Cl—Cl bond dissociation energy was estimated at 54 kcal./mole.

It is rather strange that in a preliminary communication H. von Wartenberg and F. A. Henglein (211), reporting the above studies, claimed the value of 70 kcal./mole for $D(\text{Cl}-\text{Cl})$.

(4) N—N bond dissociation energy in N_2O_4

The first experimental data on the equilibrium $\text{N}_2\text{O}_4 \rightleftharpoons 2\text{NO}_2$ were reported by E. Natanson and L. Natanson (120) in 1886, and used by K. Schreber (160) for the calculation of the heat of dissociation of N_2O_4 , estimated by him at 13.1 kcal./mole.

E. Wourtzel (224) reinvestigated this equilibrium in 1919. His results, concordant with those of E. and L. Natanson, led to a slightly smaller value for the heat of dissociation: namely, 12.85 kcal./mole. About the same time M. Bodenstein *et al.* (21) reexamined thoroughly the equilibrium $\text{N}_2\text{O}_4 \rightleftharpoons 2\text{NO}_2$. The experimental technique was considerably improved by using an all-glass apparatus and a spiral manometer.⁸ The final results were given for two sets of pressures, the so-called "higher" and "lower" constants. The results at the lower pressures were considered to be more reliable, since N_2O_4 does not follow the ideal gas law at pressures of the order of 1 atm. The heat of dissociation was estimated at 12.90 kcal./mole, showing a good agreement with results obtained by Wourtzel.

Bodenstein observed some displacement in the equilibrium $\text{N}_2\text{O}_4 \rightleftharpoons 2\text{NO}_2$ at higher temperatures (about 500°C.), and succeeded in proving that this was due to the reversible reaction $2\text{NO}_2 \rightleftharpoons 2\text{NO} + \text{O}_2$, which became appreciable at these temperatures.

⁷ Hydrogen was formed by the decomposition of water vapor present in the laboratory air, while in contact with the hot silica surface.

⁸ The previous workers used greased stopcocks, rubber tubing for connections, and mercury manometers. All these materials are attacked by nitrogen dioxide vapor, and therefore their presence in the system introduces a considerable element of uncertainty in the interpretation of results.

The deviation of N_2O_4 from the ideal gas behavior is the source of some error in Bodenstein's computation of the heat of dissociation of N_2O_4 . In order to remove this uncertainty F. Verhoek and F. Daniels (207) reinvestigated the equilibrium $N_2O_4 \rightleftharpoons 2NO_2$, using a very sensitive glass-membrane manometer, and measured the equilibrium constants for decreasing pressures. They extrapolated the results to zero pressure, thus computing the heat of dissociation at zero pressure. The measurements were taken at 25.0° , 35.0° , and $45.0^\circ C.$, in order to avoid any complications due to the decomposition of nitrogen dioxide. It was definitely proved that the presence of inert gases was without any influence on the equilibrium constant. The "corrected" heat of dissociation was estimated at 14.5–14.7 kcal./mole, i.e., considerably higher than the values proposed by previous workers.

Lastly it is necessary to consider which of the bonds is ruptured during the decomposition of the N_2O_4 molecule into NO_2 . From the study of symmetry properties of the infrared absorption spectrum of N_2O_4 L. Harris and G. W. King (73) concluded that only those models where the NO_2 groups are joined by the nitrogen atoms would be compatible with the observed pattern. This conclusion is further supported by investigation of the electron diffraction of N_2O_4 , which indicates that the N—N distance in the model $O_2N—NO_2$ is 1.6–1.7 Å. (L. R. Maxwell, V. M. Mosley, and L. S. Deming (109)). The results were confirmed by recent x-ray studies of N_2O_4 crystals (28). It is reasonable to conclude, therefore, that the fission takes place at the N—N bond and the observed heat of dissociation measures the N—N bond dissociation energy in N_2O_4 .

(5) N—N bond dissociation energy in N_2O_3

The equilibrium $N_2O_3 \rightleftharpoons NO + NO_2$ was investigated at about the same time by E. Abel and J. Proisl (1) and by F. Verhoek and F. Daniels (207). The investigation was complicated by the fact that the above equilibrium takes place simultaneously with the equilibrium $2NO_2 \rightleftharpoons N_2O_4$, the system investigated being thus composed of the four species NO , NO_2 , N_2O_3 , and N_2O_4 .

The heat of dissociation of N_2O_3 , calculated from the van't Hoff isochore on the basis of data at $25^\circ C.$ and $35^\circ C.$ and extrapolated to zero pressure, was estimated by Verhoek and Daniels at 10 kcal./mole. The results obtained by Abel and Proisl pointed to the same value (9.5 kcal./mole).

D. Other static methods used for the determination of bond dissociation energies

It was shown in Section II that the static manometric method is not suitable for the determination of very small fractions of decomposition, since the results of computation are obtained as minute differences of large numbers derived from the direct measurements. To measure accurately the small extent of dissociation it is necessary to determine, by some direct method, the concentrations of the fragments formed in the process. This can be achieved either by a colorimetric method (if the respective fragment has an intense color) or by a magnetic method (utilizing the fact that the radicals are paramagnetic). Hexaphenylethane can serve as an example for both methods.

The first colorimetric estimation of the degree of dissociation of hexaphenylethane was due to J. Piccard (134) in 1911. The method was further elaborated and improved by K. Ziegler and L. Ewald (228), who determined the dissociation constants of the equilibrium



in various solvents and over a range of temperature. Their results are listed in table 2.

Since the heat of dissociation appeared to be constant in all solvents it was concluded that it corresponds to the C—C bond dissociation energy in

TABLE 2
Dissociation of hexaphenylethane

SOLVENT	DISSOCIATION CONSTANT AT 20°C.	HEAT OF DISSOCIATION kcal./mole
Propionitrile	1.2×10^{-4}	11.1
Ethyl benzoate	1.67×10^{-4}	12.0
Acetophenone	1.70×10^{-4}	11.5
Dioxane	2.5×10^{-4}	11.6
Bromobenzene	3.7×10^{-4}	11.5
Ethylene dibromide	3.9×10^{-4}	11.4
Benzene	4.1×10^{-4}	11.3
Chloroform	6.9×10^{-4}	10.5
Carbon disulfide	19.2×10^{-4}	11.0

TABLE 3
Dissociation of hexaphenylethane

TEMPERATURE	DISSOCIATION CONSTANT	HEAT OF DISSOCIATION kcal./mole
°C.		
23	1.5×10^{-4}	
75	53×10^{-4}	11.6 ± 1.7

hexaphenylethane: $D[(C_6H_5)_2C-C(C_6H_5)_3] = 11.3 \pm 1$ kcal./mole. It must be emphasized, however, that the conclusions drawn from experiments carried out in the liquid phase are always uncertain, owing to the thermal effects connected with the solvation phenomena.

E. Müller and I. Müller-Rodloff (117) investigated the equilibrium $(C_6H_5)_2CC(C_6H_5)_3 \rightleftharpoons 2(C_6H_5)_3C^{\bullet}$ by measuring the magnetic susceptibility of the benzene solution. Although the equilibrium constants determined by these workers were smaller than those reported by Ziegler and Ewald, the heat of dissociation was found to be the same as that given by Ziegler (see table 3).

M. F. Roy and C. S. Marvel (158) reinvestigated the above dissociation process, using a magnetic method. Their results were in good agreement with Müller's observations, but later investigations of Marvel *et al.* (108) proved that

the dissociation processes of many derivatives of hexaphenylethane were followed by some irreversible reactions which consumed the radicals produced. Thus, it was found that the paramagnetic susceptibility of solutions of these compounds was falling gradually with time, attaining eventually zero value. The true estimation of the degree of dissociation required, therefore, the determination of the magnetic susceptibility as a function of time and its extrapolation to zero time. In this way the degree of dissociation of a number of hexaphenylethane derivatives was determined. It is worth mentioning that although the paramagnetic susceptibility of the solutions disappeared, their color persisted. This observation casts doubt on the results obtained by the colorimetric method. Hexaphenylethane seems to be an exceptional case, since the triphenylmethyl radicals are not removed by the irreversible process mentioned above.

The studies of Marvel were continued by R. Preckel and P. W. Selwood (139). These workers estimated the heat of dissociation of several hexaphenylethane derivatives, measuring the degree of dissociation at various temperatures by a

TABLE 4
Dissociation of hexaphenylethane derivatives

ETHANE DERIVATIVE	TEMPERATURE RANGE	ΔH kcal./mole	STABILITY
		°C.	
Hexaphenyl.....	30-80	9.9	Stable
Di(<i>o</i> -tolyl)tetraphenyl.....	10-50	11.4	Labile
Di(<i>α</i> -naphthyl)tetraphenyl.....	-10-50	11.5	Labile

magnetic method and extrapolating the results to zero time. Their results are listed in table 4. They confirmed the great stability of triphenylmethyl radicals, although they found that at 100°C. even these radicals began to disappear, and thus the paramagnetic susceptibility was approaching zero after solution had been heated for 24 hr.

E. The bond dissociation energies of some diatomic metallic molecules

The dissociation energy of a variety of diatomic molecules composed of metal atoms has been estimated by measuring the changes in the intensity of the absorption bands of these molecules caused by the variation of the temperature. In principle, there is no difference between this method and the colorimetric method discussed in connection with the dissociation process of hexaphenylethane. The only peculiarity of the metal vapor system is the minute concentration of molecules as compared with the concentration of the atoms, and the former would therefore be considered as the labile species. Owing to the low dissociation energies of such molecules the measurements must be carried out over a large temperature range, of several hundred degrees. Difficulties are frequently caused by the low volatility of metals (e.g., cadmium) and compel the investigators to resort to long absorption cells. The type of investigation which has been carried out is illustrated by the following examples.

In 1925 E. Koernicke (92) published his results of the investigation of the 2540 Å. band which appears in the absorption spectrum of mercury. He demonstrated that this band is due to the presence of Hg_2 molecules in the mercury vapor, and by measuring the intensity of the band at various temperatures and under different pressures of mercury he estimated $D(Hg-Hg)$ at 1.4 kcal./mole.

His work was repeated by H. Kuhn and K. Freudenberg (94), who measured the intensity of the 2540 Å. band at temperatures ranging from 500°C. to 1150°C. Their results were essentially concordant with those of Koernicke, and they recommended the value of 1.6 kcal./mole for $D(Hg-Hg)$.

In 1944 this work was investigated again by J. G. Winans and M. P. Heitz (220), who calculated the dissociation energy of Hg_2 from measurements of the intensity of the 2345 bands by applying the Gibson-Heitler equation (64). This result was in agreement with those of previous investigators and yielded $D(Hg-Hg) = 1.38 \pm 0.07$ kcal./mole.

Following the work of S. Mrozowski (116), who demonstrated that the absorption band at 3178 Å. is due to the Cd_2 molecule, H. Kuhn and S. Arrhenius (93) measured the changes of the intensity of this band in the temperature region 1000–1450°K. The cadmium vapor was contained in a silica tube 60 cm. long heated by a special electric furnace. Their conclusion was that $D(Cd-Cd) = 2 \pm 0.5$ kcal./mole.

For some metallic molecules it was possible to deduce the heat of dissociation from the measurements of the vapor pressure and density of the respective metal vapors. For example, the investigations of the sodium vapor pressure-temperature relationship by W. H. Rodebush and E. G. Walters (155) and by R. Ladenburg and E. Thiele (95) proved the existence of Na_2 molecules in the vapor phase and according to E. Thiele (204) $P_{Na_2} = 119$ mm. of mercury at the boiling point of sodium. From these measurements $D(Na-Na)$ was estimated at about 18 kcal./mole.

F. The equilibrium flow technique

It was mentioned in Section III,A that the occurrence of various irreversible processes, which may take place in an investigated system, is the source of the main difficulties encountered in the determination of bond dissociation energies by an equilibrium method. These processes are particularly likely to occur at high temperatures and when the period of heating is long. It is desirable, therefore, to reduce the time of heating as much as possible. The application of the flow technique is particularly advantageous in this respect.

In the flow technique the compound investigated passes through a heated reaction vessel, and the "time of contact" (i.e., the time during which the compound investigated is heated) may be varied by the proper adjustment of the rate of flow. The time of contact must be sufficiently long to enable the system under investigation to attain full equilibrium; however, this restriction is not a serious one, since the equilibrium state is attained in an extremely short period of time. Consequently, a stationary state is maintained in the reaction vessel over any required period of time, during which the determination of the relevant concentrations can be accomplished. The normal procedure is to determine by

some photometric method the concentration of the radicals (or atoms) produced by the dissociation process. The change of the radical concentration with the temperature makes it possible to determine the heat of dissociation and hence the bond dissociation energy. The method may be illustrated by two examples: the study of the equilibrium between $(CN)_2$ and CN radicals and the study of the system $2H_2O + O_2 \rightleftharpoons 4OH$.

G. B. Kistiakowsky and H. Gershinowitz were the first to investigate the equilibrium $(CN)_2 \rightleftharpoons 2CN$ (87). Cyanogen was made to flow through a silica tube 60 cm. long heated electrically to the required temperature. The concentration of CN radicals was measured by the intensity of the $O \rightarrow O$ band at 3883 Å., due to the transition $2\Sigma \rightarrow 2\Sigma^*$. The measurements were carried out over a temperature range of about $110^\circ C.$ (1124 – $1238^\circ C.$). The heat of dissociation was calculated at 77 ± 4 kcal./mole.

The problem was reinvestigated by J. U. White (216), who pointed out how misleading the photometric determination of the CN concentration would be if the results were not corrected for the incomplete resolution of the spectrograph. From the lower limit of the absolute absorption coefficient of CN radicals he calculated their partial pressure at $1500^\circ K.$ and from this data the equilibrium constant $K_{1500^\circ K.} = 1.1 \times 10^{-12}$. A lower limit for the heat of reaction follows directly from calculations based on the partition functions of $(CN)_2$ and CN radicals. Thus the most probable value of the heat of dissociation of cyanogen was computed from these data at 146 ± 4 kcal./mole, a value which is obviously widely different from that obtained by Kistiakowsky and Gershinowitz.

There is little doubt that the Kistiakowsky and Gershinowitz value is too low, but it is by no means certain that White's value is correct. White's results have been criticized by G. Herzberg (79), who pointed out that they are less direct than those obtained by Kistiakowsky and Gershinowitz, as they are dependent on the determination of the partition function of $(CN)_2$. The investigations of the kinetics of hydrogenation of cyanogen by N. C. Robertson and R. N. Pease (152) seem to point to some value in between the two earlier ones, i.e., 120–130 kcal./mole; this is further supported by some photochemical studies of T. R. Hogness and Liu-Sheng Ts'ai (84). The whole controversy has recently been reviewed by H. D. Springall (165) and by L. H. Long (104).

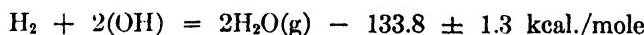
The equilibrium $2H_2O + O_2 \rightleftharpoons 4OH$ was investigated for the first time by K. F. Bonhoeffer and H. Reichardt (25). This work followed the study of K. F. Bonhoeffer (23), who demonstrated qualitatively that the dissociation of water vapor takes place according to the equation $2H_2O \rightarrow H_2 + 2OH$ (the presence of OH radicals was demonstrated by the appearance of their absorption bands). They found that the latter equilibrium could be shifted by introducing oxygen into the heated steam, and thus they were able to maintain a constant concentration of OH radicals at various temperatures of the reaction vessel, by adjusting properly the partial pressure of oxygen. Using this technique Bonhoeffer and Reichardt estimated the relative equilibrium constants of the above reaction over temperatures ranging from $1200^\circ C.$ to $1600^\circ C.$ They concluded that $D(HO-H)$ is about 115 ± 2.5 kcal./mole.

The above work was repeated very carefully by R. J. Dwyer and O. Olden-

berg (50). Also these workers pointed out the systematic errors due to the lack of the resolving power of the spectrograph. For a quantitative test by the absorption spectrum rather weak absorption is desired, and although the average absorption observed with a spectrograph of poor resolving power may be weak, the actual absorption band contains many lines, each one of which at its middle almost completely absorbs the incident radiation. The above workers used, therefore, in their studies a spectrograph of high resolving power which allowed them to measure the absorption of single lines, and by matching the absorptions of two lines of equal intensity they tested the two reacting mixtures for equal density of OH radicals. The measurement of the intensity of a single line made it possible to observe the OH radicals at lower temperatures than those used by Bonhoeffer and Reichardt (the highest temperature being brought down from 1590°C. to 1100°C.), and thus to reduce considerably many technical difficulties caused by the extremely high temperatures.

The results were corrected for (a) the nonuniform temperature distribution, (b) the difference in the Boltzmann distribution between the two temperatures, i.e., the change in the population of the various rotational levels caused by the change of temperature, and (c) the variation ΔH_T over the temperature range T_1-T_2 . The only source of systematic error which was known to the above workers was due to variations in the width of the line. The Doppler effect was responsible for one-third of the observed width of the line (126), the other two-thirds representing the pressure broadening. The pressure was of the order of 1 atm., but it was due to a mixture of water vapor and oxygen in various proportions. The observations, however, showed that the broadening effect of O₂ and H₂O on the absorption lines of OH was practically the same.

As a result of this very careful piece of work Dwyer and Oldenberg were led to conclude that



This result, in conjunction with $D(\text{H}-\text{H}) = 102.48 \text{ kcal./mole}$ as computed by H. Beutler (18), led them to $D(\text{HO}-\text{H}) = 118.2 \pm 0.7 \text{ kcal./mole}$. If instead we use $D(\text{H}-\text{H}) = 103.22$, as recommended by A. G. Gaydon (60), we obtain $D(\text{HO}-\text{H}) = 118.5 \pm 0.7 \text{ kcal./mole}$. This value leads to $D(\text{O}-\text{H}) = 101 \text{ kcal./mole}$.

The various methods of determination of $D(\text{H}-\text{OH})$ have been reviewed recently by O. Oldenberg (125).

G. The effusion method

The laws of gas effusion through an orifice the diameter of which is small in comparison with the mean free path of a molecule have been worked out by Knudsen (89), who deduced that the mass m of a gas which effuses in time t through an orifice of cross-sectional area A is given by

$$m = \frac{1}{4} (N_1 - N_2) \cdot \frac{M}{N_0} \cdot \bar{u}At$$

where N_1 and N_2 denote the number of molecules per milliliter present on each side of a membrane, respectively, M is the molecular weight of the gas, N_0 is the Avogadro number, and \bar{u} is the mean thermal velocity of the molecules. Where the gas concentration on one side of an orifice may be neglected in comparison with the concentration on the other side, then:

$$m = \frac{1}{4} \cdot N_1 \cdot \frac{M}{N_0} \cdot \bar{u}At$$

A determination of the rate of effusion makes it possible therefore to estimate the pressure of the gas (which is proportional to N_1) if the molecular weight is known, or to estimate the molecular weight if the pressure is known. Thus, for example, Knudsen determined the vapor pressure of mercury (90), and by means of similar measurements the vapor pressures of zinc, cadmium, and other metals (see, for example, Egerton (51)) were measured.

It is simple to prove that for a mixture of gases effusing through an orifice, the rate of effusion of each component is equal to its rate of effusion if it were present alone and at a pressure equal to its partial pressure in the mixture. This relationship holds, of course, only if the mean free path of the molecules in the mixture is large in comparison to the diameter of the orifice. It is possible, therefore, to use the phenomenon of effusion to estimate the mean molecular weight of partially dissociated gas. Consideration of Knudsen's formula shows that the rate of effusion is proportional to the average thermal velocity of the molecules and the latter is inversely proportional to the square root of its molecular weight. Therefore, if the pressure of the gas is kept constant, then the rates of effusion of an undisassociated and fully dissociated gas would be in the ratio of $1:\sqrt{2}$. It must be pointed out that the greatest possible change in the rate of effusion, due to the dissociation process, amounts to about 40 per cent only. Hence it is essential to determine the rates of effusion very accurately if we are to obtain reliable data on the degree of dissociation. The latter can be evaluated by using a formula which is derived from Knudsen's formula:

$$m = (M/2\pi \cdot RT)^{1/2} \cdot AtP \cdot (1 - \alpha + \sqrt{2}\alpha)/(1 + \alpha)$$

m , M , A , and t have the meanings given before, while R denotes the gas constant, T the absolute temperature of the space surrounding the orifice, P the total pressure of the gas (assuming that its pressure on the other side of the orifice is negligible), and α the degree of dissociation.

The actual performance of the experiment requires the fulfillment of several conditions which have been discussed by H. Weide and F. R. Bichowsky (213): (1) the hole must be small in comparison with the mean free path of the gas and the thickness of the plate in which it is made must be small in comparison with the diameter of the hole (the recommended thickness of the plate is 0.1 of the diameter of the orifice); (2) the chamber on the high-pressure side of the hole must be large in comparison with the mean free path of the gas; (3) the gas on the high-pressure side must be in thermal and pressure equilibrium over a region

which is in the neighborhood of the hole and large in comparison with the mean free path of the gas.

The last condition requires that the rate of effusion should be small in comparison with the rate of diffusion of the gas from its source to the space which is near the orifice. This means that the "time of contact," i.e., the average time spent by the molecules of the gas in the heated chamber which is near the hole, cannot be too short. This is rather unfortunate, because it favors the occurrence of the side reactions discussed in Section III,A.

The effusion method is, therefore, less suitable than the equilibrium flow technique in the investigations of the dissociation process $R_2 \rightleftharpoons 2R$, in which R is a radical, particularly if the temperature required to break the R—R bond is high and the radical R has not a great thermal stability. It is worth noting that the low pressure which is used in the effusion technique makes it possible to work at lower temperatures, but on the other hand it is necessary to have a high degree of dissociation (not less than about 30 per cent) in order to obtain reliable results, and that requires higher temperatures. However, the effusion method seems to compete well with the static manometric method in the region of low pressures. It was mentioned earlier (see page 86) that the great difficulty encountered in the static manometric method in the low-pressure region is due to the adsorption of radicals or molecules on the walls of the reaction vessel, and this difficulty is amplified if there is some corrosion of the wall. These effects are of no importance in the effusion method,⁹ since only the amount of substance which effuses is measured and one is not concerned with the amount of substance introduced into the reaction vessel. The following example makes this point clearer. Let us say that the heat of dissociation of fluorine is to be measured. The gas attacks the walls of most reaction vessels, particularly at high temperature. The investigation should be carried out, therefore, at low temperatures (let us say in the region of 400°C.), and in order to obtain a measurable degree of dissociation it is necessary to work at very low pressures. The manometric method seems to be of no great use, because of the corrosion of the wall which is unavoidable in this case. On the other hand, the effusion method may be used, since it requires only that a constant low pressure be maintained on one side of the hole and that the quantity of effused fluorine be measured. The corrosion of the vessel walls is of no importance, with the exception of the slight change in diameter of the orifice, for which a correction may be introduced based on measurements of its cross-sectional area before and after each experiment.

The effusion method was used by T. DeVries and W. H. Rodebush (45) in the determination of the dissociation energies of iodine and bromine. Great stress was laid upon the necessity of maintaining a constant pressure in the apparatus. For example, the pressure of iodine was kept constant by having a reservoir of iodine crystals maintained at a constant temperature of ice water, and it was pointed out that variations of temperature of a few hundredths of a degree would change the vapor pressure sufficiently to make a determination worthless.

* In the case when corrosion of the wall produces volatile materials the required correction must be introduced by analyzing the composition of the substance which has effused.

Special precautions were taken to avoid changes of vapor pressure caused by the distillation of the smaller crystals on to the larger ones, and attention was called to the conditions under which there is satisfactory thermal contact between the crystals and the external wall of the reservoir.

The various technical difficulties were adequately resolved in the case of iodine, but a less satisfactory solution was achieved in the case of bromine. These authors estimated $D(I-I)$ at 31.6 kcal./mole and $D(Br-Br)$ at 41.2 kcal./mole. Both values seem to be too low by a few kilocalories per mole.

E. Wrede (223) suggested the following modification of the effusion method: Two compartments are divided by a wall perforated by one or several orifices. Owing to some dissociation process, there is a mixture of undissociated and dissociated species in one compartment, while there is a full recombination in the second compartment. In consequence, there is a stationary difference in pressures on both sides of the orifice which measures the degree of dissociation. This method is not suitable for the estimation of the degree of thermal dissociation, since by keeping both compartments at different temperatures additional difference of pressures is introduced which decreases the sensitivity of the method.

H. The hot wire method

The characteristic feature of the hot wire method is the mode by which the heat is supplied to the molecules which eventually dissociate. In the experimental arrangement the molecules of the gas investigated strike the surface of a hot wire, heated to the required temperature, and in consequence of these impacts they may dissociate into some fragments. The actual process of dissociation is investigated either by measuring the amount of heat carried away from the wire (the conductometric method), or by determining the rate of the dissociation process (the thermal equilibrium method).

The conductometric method was developed by the pioneer work of I. Langmuir (97), who made the observation that a layer of stationary gas seems to surround a hot wire, and that the heat carried away from the wire through this layer is transferred by a pure conduction process and not by a convection process. The amount of heat removed by conduction is determined as the difference between the amounts of heat lost by the wire when surrounded by the gas investigated and when heated in the high vacuum, provided of course that the temperature of the wire is the same in both cases. According to Langmuir the heat carried away by the conduction process may be calculated by the following formula

$$W_e = S(\varphi_2 - \varphi_1)$$

where W_e denotes the rate of heat loss from a unit surface of the wire, S (called by Langmuir the shape factor) is a coefficient which depends on the geometry of the lamp and the nature of the gas, and φ_2 and φ_1 are functions of the temperatures of the wire and the cooling agent, respectively. Further considerations of this phenomenon led Langmuir to the following expressions for S , φ_2 , and φ_1 :

$$S = \text{const. } 2\pi/\ln(b/a)$$

b denoting the thickness of the stationary layer of gas which surrounds the wire and a denoting the diameter of the wire, while the constant depends on the units used in the computation.

$$\varphi_2 = \int_0^{T_2} k \, dT; \quad \varphi_1 = \int_0^{T_1} k \, dT$$

where T_2 and T_1 denote the temperatures of the wire and the cooling agent, respectively, and k denotes the specific conductivity of the gas investigated.

Langmuir deduced also that $b \ln(b/a)$ is a constant which depends on the nature and pressure of the gas investigated but is independent of the diameter and the temperature of the wire. All these theoretical deductions he confirmed by a series of accurate measurements of the heat lost by wires maintained at various temperatures and surrounded by a variety of gases under various pressures.

The above treatment requires, however, some modification if the gas investigated dissociates on the surface of the wire. The theory of the heat conduction in a dissociating gas was also developed by Langmuir and reported in a subsequent paper (98). The heat carried away from the wire (deducting the loss due to radiation) was represented by:

$$W = W_c + W_d$$

W_c having the same meaning as before, while W_d represents the amount of heat carried away by the dissociating particles during the process of dissociation. This heat is subsequently transferred to the cooling agent during the recombination process. For the sake of clarity we restrict this discussion to the dissociation of hydrogen on a hot wire. The hydrogen atoms produced in the dissociation process diffuse away from the immediate vicinity of the wire to the outside, the rate of the diffusion being dependent on the gradient of concentration, dc/dx . Assuming that c is given by the *equilibrium concentration* of hydrogen atoms determined by the temperature corresponding to the appropriate point in the stationary layer of the gas surrounding the hot wire, and taking into account that each gram-atom of hydrogen disappearing from the gas phase produced $\frac{1}{2}Q$ kcal. (Q being the heat of dissociation $H_2 \rightleftharpoons 2H$), Langmuir concluded that

$$W_d = \frac{1}{2} Q S c_0 D$$

c_0 denoting the initial concentration of hydrogen atoms in the immediate vicinity of the wire and D being the diffusion constant of hydrogen atoms in a medium of hydrogen molecules. W_d is calculated from the total observable heat lost (W) and the extrapolated value of W_c , using for the extrapolation the values obtained for $W \approx W_c$ in the temperature region in which the dissociation is negligible.

If c_0 is equal to the equilibrium concentration of hydrogen atoms corresponding to the temperature of the wire, then it is possible to calculate Q from the temperature dependence of W_d . This type of calculation led Langmuir to the conclusion that $D(H-H)$ is about 130 kcal./mole.

The method described here was criticized by Langmuir (99) himself, who em-

phasized the doubtful nature of two assumptions involved in the deduction: (a) the assumption that the gas in the vicinity of the wire attains the same temperature as the wire and that c_0 is equal to the equilibrium concentration of hydrogen atoms at this temperature; and (b) the assumption that the shape factor S remains the same over the whole temperature range, the latter assumption being a particularly great source of error, since the calculated value of Q is extremely sensitive to small changes in S (it affects both the calculated value of W_D from $W - W_c$, and the value of dW_D/dT). Langmuir developed therefore an alternative treatment (99), in which allowances were made for accommodation coefficients different from 1 by introducing two constants α_1 and α_2 , which denote the fractions of hydrogen atoms and hydrogen molecules adsorbed on the wire. Assumption (b) was also avoided by deriving a formula for the equilibrium constant

$$K = \frac{(W/Q)^2(P/D + 1/\alpha_1)^2}{P - (W/Q)(P/D - 1/\alpha_2)^2}$$

and choosing the "best" set of values for the constants K , D , α_1 , and α_2 , i.e., for which the best agreement was obtained between the calculated and observed values of W corresponding to various pressures P . This treatment yielded a value of 84 kcal./mole for Q (at constant volume) and 90 kcal./mole (for constant pressure).

The method can be simplified considerably if one determines directly the rate of the dissociation process. This can be achieved if every atom produced by the dissociation process is trapped and removed from the system. This was the case in the experiments performed by G. Bryce (32). A tungsten wire was heated in hydrogen maintained under a pressure sufficiently low to enable every hydrogen atom emitted from the hot wire to be adsorbed on the surface of molybdenum oxide. Thus the rate of dissociation was measured by the rate of decrease of pressure due to the adsorption of hydrogen atoms.

The data obtained in this way may be utilized in two ways. One determines the loss of heat from the wire and by extrapolation estimates the loss due to the undissociated molecules (using for the extrapolation the data obtained at the temperatures at which the dissociation is negligible). Thus the heat transferred by the atoms is computable, and, their number being known, the dissociation energy may be deduced. The calculation requires, however, a correction for the kinetic energy of the atoms, which would only be calculable if the accommodation coefficient is 1.

The second possibility is to assume that the accommodation coefficient is 1. The numbers of molecules and atoms leaving the wire would then obey the equilibrium condition. Since the total mass of particles leaving the wire must be equal to the mass of hydrogen molecules striking the wire, and the latter is given by the kinetic theory if we know the pressure and temperature of the gas in the tube, then the estimation of the mass of hydrogen atoms produced leads directly to the equilibrium constant for $H_2 \rightleftharpoons 2H$ dissociation at the temperature of the wire. P. M. Doty (47), using the experimental results of Bryce (32),

demonstrated that the calculated equilibrium constant, on the assumption of an accommodation coefficient equal to 1, agreed fairly well with the value derived from spectroscopic data. He concluded, therefore, that in this case the accommodation coefficient is indeed equal to 1. The equilibrium constant being known, the heat of dissociation may be calculated by applying the equation of the van't Hoff isochore.

An interesting modification of the hot wire technique was introduced by P. P. Sutton and J. E. Mayer (181). They developed a device which made it possible to measure the current due to the flow of electrons and negative ions emitted from the hot wire. Moreover, this device enabled them to estimate separately the extent to which both species participated in the current measured. The results obtained in this way were used by Mayer and his colleagues for the estimation of the electron affinity of chlorine (105, 115), bromine (49), iodine (181), and oxygen (112, 208). The method of computation was based on the *assumption* that the accommodation coefficient of the molecules used in these experiments was equal to 1, and the final results provided a fair *a posteriori* justification for this assumption.

P. M. Doty (48) applied the above method to the determination of the C—Cl bond dissociation energy in methyl chloride and carbon tetrachloride. If the accommodation coefficient is 1, then the molecules of methyl chloride striking the surface of the hot wire would attain thermal equilibrium. That is to say, the number of methyl radicals, chlorine atoms, and undissociated molecules of methyl chloride leaving a unit surface of the wire in every second would be equal to the number of the respective species hitting this surface in a unit of time, provided the wire is in an atmosphere of a hypothetical gas composed of CH_3 , Cl, and CH_3Cl in an equilibrium corresponding to the temperature of the wire. We calculate the number of molecules hitting the unit surface, using the formula provided by the kinetic theory of gases:

$$Z_{\text{CH}_3} = \frac{P_{\text{CH}_3}}{(2\pi M_{\text{CH}_3} k T_s)^{1/2}}; \quad Z_{\text{Cl}} = \frac{P_{\text{Cl}}}{(2\pi M_{\text{Cl}} k T_s)^{1/2}};$$

$$Z_{\text{CH}_3\text{Cl}} = \frac{P_{\text{CH}_3\text{Cl}}}{(2\pi M_{\text{CH}_3\text{Cl}} k T_s)^{1/2}}$$

Taking $P_{\text{CH}_3} = P_{\text{Cl}}$ and knowing that the total mass of the species leaving the wire must be equal to the mass of methyl chloride molecules *actually* striking the wire (the latter is obtained from the pressure and temperature of methyl chloride introduced to the apparatus), we calculate the equilibrium constant, K_1 ,

$$K_1 = \frac{(P_{\text{Cl}})^2}{P_{\text{CH}_3\text{Cl}}}$$

in terms of one unknown only, that is, P_{Cl} . Now the chlorine atoms are in equilibrium with the chloride ions and electrons and thus

$$K_2 = \frac{P_{\text{Cl}^-}}{P_{\text{Cl}} \cdot P_e}$$

P_{Cl^-} and P_e denoting the partial pressures of the hypothetical chloride ions and electron gases which are in thermal equilibrium with chlorine atoms. Since P_{Cl^-} is much smaller than P_{Cl} , the second equilibrium does not affect the first one. The ratio P_{Cl^-}/P_e is computed from the ratio of i_{Cl^-}/i_e , i_{Cl^-} and i_e denoting the currents due to the flow of chloride ions and electrons, respectively.

$$P_{\text{Cl}^-}/P_e = (i_{\text{Cl}^-}/i_e) \cdot (M_{\text{Cl}}/M_e)^{1/2}$$

M_{Cl} and M_e being the masses of the chlorine atom and the electron, respectively.

One concludes therefore that:

$$P_{\text{Cl}} = (i_{\text{Cl}^-}/i_e)(M_{\text{Cl}}/M_e)^{1/2} \cdot K_2^{-1}$$

Since K_2 is given by the known partition functions of electrons, chlorine atoms, and chloride ions, in conjunction with the known electron affinity of chlorine atoms, the measurement of i_{Cl^-}/i_e determines P_{Cl} , and by that K_1 . The determination of the heat of dissociation is then straightforward.

Again it must be emphasized that all the methods discussed above are based on the assumption of accommodation coefficients equal to 1. Doty found, however, that the accommodation coefficients for both methyl chloride and carbon tetrachloride were appreciably smaller than 1. In spite of that he obtained a good straight line by plotting the logarithm of the quasi-equilibrium constant against $1/T$, and he concluded therefore that the "apparent" heat of reaction, given by the slope of this line, was identical with the "true" heat of reaction. His confidence was increased by the fact that the "apparent" heat of reaction estimated by him at 74 kcal./mole was well within the range of the "bond energies" of the C—Cl bond as quoted by Pauling at 66.5 kcal./mole (132) and by O. K. Rice at 73 kcal./mole (149). These values, however, represent the "average bond energy," while Doty tried to estimate the bond dissociation energy. The latter seems to be 80–81 kcal./mole, as computed from the heats of formation of methyl chloride and the methyl radical, respectively. It seems, therefore, that the results obtained from the quasi-equilibrium constant should be regarded with a good deal of suspicion.

I. The molecular beam method

If some molecule, say X_2 , dissociates into $2X$, then one may estimate the relative concentrations of X_2 and X in the equilibrium mixture by applying a molecular beam technique (see R. G. J. Fraser (59)). The investigation may be carried out either by separating atoms and molecules with the aid of a magnetic field and counting both species separately, or by investigating the velocity distribution in the beam.

The separation of the atoms and molecules in a mixed beam can be effected if the molecules are diamagnetic while the atoms have a magnetic moment. Performing a Stern-Gerlach experiment (63) on a mixed atomic-molecular beam one deflects the atoms right and left without influencing the molecules, which are unaffected by the field.

The first observations of this kind were made on bismuth by A. Leu (101),

who measured the temperature dependence of the line which corresponded to Bi_2 molecules, and thus deduced that $D(\text{Bi}-\text{Bi}) = 56 \text{ kcal./mole}$. This result was very rough, and in addition R. G. J. Fraser pointed out (63) that Leu made several mistakes in his interpretation of the experimental observations. Corrections introduced by Fraser reduced the value of $D(\text{Bi}-\text{Bi})$ to $26 \pm 12 \text{ kcal./mole}$.

The technique was developed further by L. C. Lewis (103), who examined the dissociation energies of Li_2 , Na_2 , and K_2 . His results are given in table 5. This work was repeated by W. Meissner and H. Scheffers (110), whose results checked those obtained by Lewis within 5 per cent.

The velocity distribution method applies the slotted-disc velocity sectors devised by B. Lammert (96), which make it possible to estimate the relative amount of molecules (or atoms) moving with some definite velocity. If the beam is composed of one species only, the plot of the fraction of the species moving with velocity v against v produces one maximum only which corresponds to the most probable velocity. If, however, two species are present in the beam, e.g.,

TABLE 5
Dissociation energies of alkali metal molecules determined by molecular beam method

SUBSTANCE	D_b kcal./mole
Li_2	22.7
Na_2	16.5
K_2	15.0

atoms and diatomic molecules, then the distribution curve shows two maxima. Analysis of such a curve might lead to the information required for the calculation of the bond dissociation energy.

This method was utilized by I. F. Zartman (226) for the investigation of the dissociation process $\text{Bi}_2 \rightleftharpoons 2\text{Bi}$. He concluded that under his experimental conditions, at $851^\circ\text{C}.$, the beam was composed of 40 per cent bismuth atoms and 60 per cent bismuth molecules (Bi_2).

Similar work was carried out by Cheng Chuan Ko (91). This author estimated the equilibrium constant for the dissociation process $\text{Bi}_2 \rightleftharpoons 2\text{Bi}$ by measuring the distribution curve over the temperature range 827 – 947°C . The total pressure was estimated by an independent measurement of the rate of effusion. The accuracy claimed by this author was 1 per cent, but the estimated $D(\text{Bi}-\text{Bi})$ at about 77 kcal./mole cast doubt as to the reliability of the method.

J. The chemiluminescence method

A very elegant method for the estimation of the bond dissociation energy of the diatomic alkali metal molecules was developed by M. Polanyi (135). His studies of reactions between highly diluted halogens and alkali metals revealed the phenomenon of chemiluminescence which was explained by the occurrence

of the reaction $\text{Cl} + \text{Na}_2 \rightarrow \text{NaCl} + \text{Na}^*$, where Na^* denotes an excited sodium atom which emits the observed radiation. The intensity of the chemiluminescence is dependent on the concentration of Na_2 molecules, and the latter decreases, of course, with increasing temperature. According to this mechanism the intensity of chemiluminescence should decrease with the overheating of the reaction zone, and the experiment confirmed fully this conclusion. The temperature dependence of the intensity of the chemiluminescence made it possible to estimate $D(\text{Na—Na})$ and the measurements by M. Polanyi and G. Schay (136) allowed them to calculate $D(\text{Na—Na})$ at 18 ± 2 kcal./mole.

This type of experiment carried out in Polanyi's laboratories by H. Ootuka made it possible to estimate $D(\text{Na—Na})$ at 19 ± 1 kcal./mole (127) and $D(\text{K—K})$ at 12.5 kcal./mole (128). These values compare favorably with the "best" values recommended by A. G. Gaydon (60): namely, $D(\text{Na—Na}) = 17.8$ kcal./mole and $D(\text{K—K}) = 11.8$ kcal./mole.

K. The explosion method

The heat liberated in the explosion of a hydrogen-oxygen mixture is used for heating a known amount of gas. Since the amount of heat liberated is known, it is possible to calculate the maximum temperature of the mixture providing the required specific heats of the components are known. The maximum temperature may be estimated from the maximum pressure developed in the combustion bomb. This is the principle of the method developed by Bunsen and by Nernst for direct measurements of the specific heats at constant volume (see, for example, A. Eucken (53)).

The estimation of the specific heat by spectroscopic methods makes it possible to compare the calculated and observable maximum temperatures. It was found that the observable temperature was frequently too low and it was assumed that the discrepancy was due to the dissociation process; e.g., $2\text{H}_2\text{O} \rightleftharpoons \text{H}_2 + 2\text{OH}$. It was feasible, therefore, to calculate the dissociation energy from the data obtained by the explosion method. This type of determination was carried out by K. Wohl and G. von Elbe (221) and K. Wohl and M. Mugat (222); the best results were obtained by B. Lewis and G. von Elbe (102), who estimated $D(\text{HO—H})$ at 114 ± 1 kcal./mole.

The method is not very reliable, and has been criticized in an article published by A. Eucken in *Handbuch der experimentalen Physik* (53).

IV. THE KINETIC METHOD OF ESTIMATING THE BOND DISSOCIATION ENERGY

A. Principles

In order to estimate the bond dissociation energy by a kinetic method, one must determine the activation energy corresponding to the *unimolecular decomposition* of the molecule into the two fragments, R' and R'' , produced by the rupture of the bond in question. It is very probable that the recombination of the fragments formed in the dissociation process does not require any activation

energy,¹⁰ and therefore it is plausible to assume that the activation energy of the dissociation process is equal to the heat of dissociation, i.e., to the bond dissociation energy.¹¹ It is found that the values of bond dissociation energies obtained by the kinetic method and based on the assumption of zero activation energy for the recombination process are self-consistent and in substantial agreement with results obtained from other direct determinations or from thermochemical data (see, for example, page 138). This provides a valuable justification of the assumption of zero activation energy for the recombination process, and strengthens our confidence in the reliability of the kinetic method. Nevertheless, it should be stressed that, if the activation of the recombination process has a finite value, then the value of the bond dissociation energy obtained by the kinetic method will be too high. In such a case it will represent only the upper limit of the "true" dissociation energy.

The required activation energy can be computed in the usual way from the temperature coefficient of the unimolecular dissociation rate constant, and in Section IV,D it is shown that this "experimental activation energy" is identical for all practical purposes with the bond dissociation energy. Although no absolute values of the rate constants are required for the computation of the temperature coefficient, it is nevertheless essential to obtain a very high degree of accuracy in estimating relative rate constants. The following example illustrates this point. The rate constants of a unimolecular dissociation were estimated at two temperatures, T_1 and T_2 , for which $1/T_1 - 1/T_2 = 10^{-4}$. This corresponds to a reasonable temperature range of about 50° if the experiments are conducted in the vicinity of 500°K., and to a range of about 100° for experiments carried out in the region of 1000°K. Let us assume that both rate constants, estimated at T_1 and T_2 , respectively, are uncertain by about 20 per cent each; then the maximum experimental error of the computed activation energy is:

$$E = 2 \times 2.3 \times \ln(1.2/0.8)/(10^{-4} \times 1000) \text{ kcal./mole} = 8.1 \text{ kcal./mole}$$

To improve the accuracy of the computed activation energy it is necessary either to extend the temperature range or to increase the accuracy of the estimated rate constants. The extension of the temperature range is limited by technical difficulties. The reaction at high or low temperatures may be unsuitable for experimentation, being either too rapid or too slow. Alternatively, the mean value of the rate constant can be made more reliable by frequent repetition of individual runs, but this leads to an improvement of the results only when the experimental errors are of the haphazard type. On the other hand, if the determination of the rate constant involves a systematic error, which is itself temperature dependent, then the deviation of the temperature coefficient, and consequently of the "activation energy," is of a permanent nature and cannot be eliminated by mere repetition of runs. Such a situation is created if, for example,

¹⁰ This problem was discussed previously in Section I,G.

¹¹ The relationship between the experimental activation energy of the unimolecular dissociation process and the bond dissociation energy is discussed in detail in Section IV,D.

the main reaction, which is the subject of investigation, is accompanied by some side reaction the relative extent of which continuously increases or decreases with the temperature. The reader will find examples of such reactions in the following sections.

It is essential, therefore, to find experimental conditions under which all side reactions are suppressed as far as possible. Only under these circumstances can one expect to be able to determine accurately the "true" activation energy of the process from the temperature coefficient of the rate constant.

B. Estimation of the bond dissociation energy if the frequency factor of the unimolecular dissociation rate constant is known

In the preceding section we have discussed the difficulties encountered in the computation of the activation energy from the temperature coefficient. Fortunately these values of the activation energy can sometimes be checked by calculating the frequency factor of the unimolecular rate constant.

The absolute rate of the truly unimolecular reaction may be expressed by:

$$k = \nu \cdot e^{-E/RT}$$

where ν , the so-called frequency factor, should have a value of the order of 10^{13} sec.⁻¹ This result was deduced for the first time by M. Polanyi and E. Wigner (137), and the subsequent development of the theory of the absolute rate constants of unimolecular reactions has provided further arguments in favor of such an order of magnitude for ν (65).

In Section IV,D the theory of the absolute rate constant of a unimolecular dissociation process is discussed further, together with experimental evidence favoring the theoretical deductions. At this point we assume that the frequency factor of a unimolecular dissociation is known, and consider the consequences of such an assumption for the problem of determining bond dissociation energies by kinetic methods.

Suppose that the frequency factor of some unimolecular dissociation is known to be 1×10^{13} sec.⁻¹ This information might be utilized in two ways:

- (a) If the temperature coefficient of the rate constant of the unimolecular dissociation has been determined, then we are able to calculate the experimental activation energy and from this the experimental frequency factor. If the latter entity comes out at about 1×10^{13} sec.⁻¹, then we have a further argument supporting the conclusion that the estimated "experimental activation energy" is the "true activation energy," i.e., is equal to the bond dissociation energy.
- (b) If the temperature coefficient of the unimolecular rate constant has not been estimated, or if it cannot be estimated owing to some technical difficulties, then we are able to calculate the "true activation energy" from the absolute value of the rate constant determined at one temperature only.

Let us illustrate the latter procedure by a numerical example. The unimolec-

ular rate constant k has been estimated at 10^{-2} sec.⁻¹ at a temperature of 800°K. From the equation:

$$k = 1 \times 10^{13} \times e^{-E/RT}$$

we derive

$$E = 2.3(13 - \log k) \cdot RT/1000 \text{ kcal./mole}$$

i.e.,

$$E = 2.3(13 + 2)2.800/1000 \text{ kcal./mole}$$

$$= 55 \text{ kcal./mole.}$$

The examination of the expression $E = 2.3(13 - \log k)RT/1000$ reveals that E is not very sensitive to experimental errors involved in the estimation of k ; e.g., an error in the latter as high as 100 per cent produces an error of only 1.1 kcal./mole in the E computed above. Furthermore, it is apparent that by using data obtained for a very slow reaction, which is carried out at the lowest possible temperature, one can reduce still further the absolute error in E computed by the above method.

It is, of course, very important to use the correct value of ν in such calculations. It is possible, however, to obtain a reasonably good result for E even though the chosen value of ν is wrong by, say, a factor of 5. Thus an error in ν by a factor of 5 produces in the above numerical example an error in E which amounts to 2.6 kcal./mole.

It is instructive to compare the magnitudes of the above errors in E with those which are involved in E calculated from the temperature coefficient of the unimolecular rate constant. In the numerical example discussed in the preceding section errors of 20 per cent in the estimated rate constants produce an error of 8.1 kcal./mole in the activation energy calculated. Therefore, if the experimental and/or theoretical evidence makes it probable that the rate of some process is approximately governed by the unimolecular dissociation, then the activation energy corresponding to this unimolecular decomposition can be estimated fairly accurately by the application of the expression:

$$E = (13 - \log k)2.3RT/1000 \text{ kcal./mole}^{12}$$

particularly if the data used in this computation correspond to a very slow reaction investigated at a comparatively low temperature. On the other hand, the activation energy computed from the temperature coefficient of the rate constant of such a reaction (which involves side reactions or consecutive reactions in addition to the main unimolecular decomposition) may be very different from the former activation energy, which would then be considered as the more re-

¹² The value of 13 was chosen on both theoretical and experimental grounds. The experimental evidence is listed in Section IV,D, and it seems to indicate that for a variety of unimolecular dissociations (caused by rupture of one bond only) the "true" values of ν do not vary by more than a factor of 5 from 10^{13} sec.⁻¹

liable. This point, fully appreciated by E. T. Butler and M. Polanyi (35), is discussed on page 123.

C. Estimation of the differences in bond dissociation energies in series of similar molecules

In Section IV,B it was shown that a fairly reliable estimate of the bond dissociation energy might be attained by a computation based on the assumed value of 10^{13} sec.⁻¹ for the frequency factor of the unimolecular decomposition. The absence of more exact knowledge of this frequency factor, however, is the cause of an error in these computed bond dissociation energies, and consequently this method fails in the detection of small variations of bond dissociation energies.

The problem could be considerably simplified by confining ourselves to the study of the variations of the dissociation energy of some particular bond, say C—X, in a series of molecules of the type RX, where R is a member of some specified class of kindred radicals. There is strong evidence that for such a series of molecules RX, the frequency factors of the unimolecular decompositions $\text{RX} \rightarrow \text{R} + \text{X}$ are identical. If this is the case then the difference $D(\text{R}'-\text{X}) - D(\text{R}''-\text{X})$, R' and R'' belonging to the same class of radicals, may be accurately estimated from the ratio of the relevant unimolecular rate constants measured at the same temperature. Thus one obtains the following expression:

$$D(\text{R}'-\text{X}) - D(\text{R}''-\text{X}) = 2.3RT \ln (k_2/k_1)$$

k_1 and k_2 denoting the respective unimolecular rate constants, both measured at temperature T .

Examination of the above expression reveals that this method of estimating variations in $D(\text{R}-\text{X})$ requires neither a knowledge of the frequency factor, nor the absolute value of the rate constants. One need only determine, as carefully as possible, the relative rate constants and ascertain that they are actually proportional to the rate constants of the *primary* dissociation process. If the latter condition is fulfilled, then one is able to detect even small differences in the relevant dissociation energies. (See, however, page 128 for an example of the misuse of this method.)

We must now examine evidence supporting the assumption of the constancy of the frequency factors in the series of unimolecular dissociations under discussion. There is evidence that in any series of reactions in which one varies the components without influencing the reaction centers (e.g., by substitution) the frequency factor (i.e., the temperature-independent factor) remains constant for the whole series.

Thus, C. K. Ingold and W. S. Nathan (85) estimated the activation energies for the hydrolysis of various substituted benzoic esters. The plot of the estimated activation energies *versus* $\log k$ (k being the rate constant of hydrolysis) gives a straight line, proving that the frequency factors remain constant throughout the whole series. These authors also drew attention to the results obtained by E. G. Williams and C. N. Hinshelwood (219) for the kinetics of benzoylation of various substituted anilines. A similar plot of E *versus* $\log k$ obtained by the latter authors

gave a straight line which was parallel to that obtained by Ingold and Nathan. The idea of the constant frequency factors in a series of kindred reactions was developed further by L. P. Hammett (70), who devised a system of σ and ρ factors; ρ represents an entropy change constant for the same type of reaction, and σ represents the change in activation energy characteristic for each member of the series.

M. Szwarc (183, 186) estimated directly the frequency factors of a series of unimolecular dissociations of the type $C_6H_5CH_3 \rightarrow C_6H_5CH_2\cdot + H$, and found that, within experimental errors, they are identical for toluene, *m*-xylene, *p*-xylene, and *o*-xylene. The tabulated frequency factors of the xylenes are halved, since the presence of two methyl groups doubles the rate of the decomposition as a purely statistical effect. The same values for the frequency factors were obtained by M. Szwarc and A. Shaw (200) for the unimolecular dissociations of methylated naphthalenes. These results are given in table 6.

TABLE 6
Dissociation of methylated benzenes and naphthalenes

COMPOUND	THE FREQUENCY FACTOR FOR THE UNIMOLECULAR DISSOCIATION $RH \rightarrow R + H$, CALCULATED PER METHYL GROUP
Toluene	$2 \times 10^{13} \text{ sec.}^{-1}$
<i>m</i> -Xylene	$2 \times 10^{13} \text{ sec.}^{-1}$
<i>p</i> -Xylene	$2.5 \times 10^{13} \text{ sec.}^{-1}$
<i>o</i> -Xylene	$2.5 \times 10^{13} \text{ sec.}^{-1}$
α -Methylnaphthalene	$1.5 \times 10^{13} \text{ sec.}^{-1}$
β -Methylnaphthalene	$1.5 \times 10^{13} \text{ sec.}^{-1}$

The direct estimation of the frequency factor is subject to some experimental error, e.g., the values quoted in table 6 are uncertain within a factor of 2-3. There is, however, a more accurate way of demonstrating the constancy of the frequency factors. It would seem that there is no relationship whatever between the frequency factor of a reaction and its activation energy. The theoretical treatment of this problem indicates that the causes of variations in activation energies and in frequency factors are to be traced to quite different sources. It is therefore extremely improbable that in a series of similar decompositions the variations in activation energy would be just balanced by the variation in frequency factor, thus leaving unchanged the rate constant of the reaction. For example, it was observed that the rate constants of the decomposition of toluene, *m*-xylene¹³ (186), the *p*-, *m*-, and *o*-fluorotoluenes (196), and γ -picoline (151) were all equal within 25 per cent. It was demonstrated that all these reactions are of the same type:



There is no reason to expect changes in the C—H bond dissociation energies in any of these compounds (see reference 196), and the equality of all these rate

constants is, in the writer's opinion, the strongest argument in favor of the assumption of the constancy of the frequency factors in a series of similar decompositions. The same conclusion follows from the results of M. Szwarc and A. Shaw (200), who found identical rate constants for the unimolecular decompositions of α -methylnaphthalene, β -methylnaphthalene, and 1,6-dimethylnaphthalene.¹³

We conclude, therefore, that there is full justification for computing the differences in bond dissociation energies caused by various substitutions in a given molecule, by comparing the relative rate constants of the respective *unimolecular* dissociation processes.

D. Theoretical treatment of unimolecular dissociation

In the theoretical treatment of unimolecular reactions we have to distinguish between two aspects of this phenomenon: activation and decomposition.

By activation we understand the process of energy transfer from the molecules of the system to some particular molecule which thus becomes "activated." This process is the result of a successful series of collisions in which the molecule eventually activated participates, and it is, therefore, essentially a bimolecular process obeying second-order kinetics. Hence the rate of activation, irrespective of the mechanism, is proportional to the partial pressure of the compound which yields the activated species and to the total pressure in the system.¹⁴ The proportionality coefficient depends on the nature of the molecules composing the system, different molecules having different specific power of accepting or transferring energy.

By decomposition we understand the process of spontaneous dissociation of the "activated" molecule into products. The probability of this dissociation is characteristic of the "activated" molecule, being independent of the total pressure. It follows, therefore, that the rate of decomposition is proportional to the concentration of "activated" molecules.

A discussion of the mechanism and rate of the energy-transfer process is beyond the scope of this paper. We assume that in all cases discussed further the rate of activation is much higher than the rate of decomposition and that most of the "activated" molecules are deactivated by subsequent collisions with surrounding molecules. This assumption, which is the basis of Lindemann's theory, leads to the conclusion that the concentration of "activated" molecules is given approximately by the equilibrium distribution of the energy of the system amongst all the molecules of which it is composed. Provided that the pressure in the system is high enough,¹⁵ the energy-transfer process will be sufficiently

¹³ The rates of decomposition of *m*-xylene and of 1,6-dimethylnaphthalene are halved, and thus they represent the "rate of decomposition per one methyl group."

¹⁴ If the system contains only one type of molecule, the rate of activation is proportional to the square of the pressure.

¹⁵ It seems that, for sufficiently complex molecules, the energy-transfer process is rapid even at pressures as low as a few millimeters of mercury. However, for small molecules containing three or four atoms, the pressure required seems to be much higher.

rapid to maintain the appropriate stationary concentration of "activated" molecules.

In order to calculate the rate of a unimolecular decomposition we apply the transition-state method. There is, however, some difficulty in defining the transition-state complex (sometimes called "activated complex"), and in this respect two different types of unimolecular decompositions should be distinguished:

1. Decompositions leading to the formation of two products, recombination of which involves an activation energy, e.g.:



2. Decompositions leading to the formation of two fragments, recombination of which requires no activation energy. This case is particularly important for us, as it covers the dissociation of the molecule into two radicals.

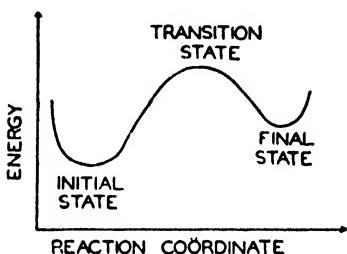


FIG. 1

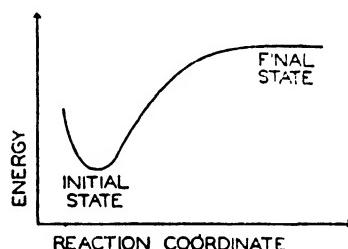


FIG. 2

In the dissociation processes of the first type we do not encounter any difficulties in the definition of the transition-state complex. On plotting the energy of the system as a function of the reaction path coördinate, one obtains the curve shown in figure 1. The hump of this curve represents the transition state which is, therefore, *completely* defined by the coördinates of this point. Figure 2, on the other hand, illustrates a decomposition of the second type, and because it does not show a hump a similar interpretation of the transition-state complex is impossible. In order to avoid the difficulties arising from the absence of a description of the transition-state complex, we adopt for the latter case a slightly modified treatment of the transition-state method, as described below.

Let us consider all the energy levels corresponding to various modes of motion of some particular bond in some particular molecule. These energy levels can be classified into two groups: (A) Energy levels which correspond to the proper vibration of the bond, i.e., for which the energy is smaller than the bond dissociation energy D^{16} (see figure 3). (B) Energy levels which correspond to the translational mode of motion, i.e., for which the energy is greater than the bond dissociation energy D^{17} . These two classes of energy levels are denoted in figure 3

¹⁶ The value of D used here is the dissociation energy *per molecule*.

¹⁷ The energy levels corresponding to the translational mode of motion could be discrete only if the motion is limited in space, i.e., if the bond is enclosed in a "box." The length of this "box" is chosen arbitrarily as ds .

by A and B, respectively. It is obvious, of course, that the bond in question can be ruptured only if it is in a state which corresponds to any energy level belonging to class B.

Let us now assume that there is no interaction between energy levels which correspond to various degrees of freedom of the molecule. For such cases, the total partition function of the molecule can be represented as:

$$f_{\text{total}} = \prod_i^n f_i$$

where f_i denotes the partition function corresponding to the i^{th} degree of freedom of the molecule. We can represent f_{total} in a slightly different way:

$$f_{\text{total}} = f' \cdot f_k$$

where $f' = \pi' f_i$ represents the product of the f_i 's for all i -values with the exception of $i = k$, and f_k represents the partition function corresponding to the vibrational degree of freedom of the bond in question.

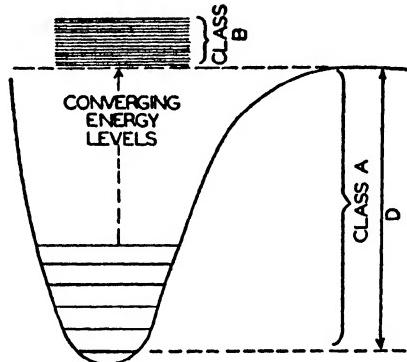


FIG. 3

The partition function f_k may be represented by:

$$f_k = \sum e^{-\epsilon_j/kT} + e^{-D/kT} \cdot f_{\text{transl}} \approx \sum e^{-\epsilon_j/kT}$$

the summation being taken over all vibrational energy levels, the j^{th} of them corresponding to the energy ϵ_j , taking $\epsilon_0 = 0$; D is the dissociation energy of the bond in question, i.e., the difference between the vibrational zero energy level and the convergence limit of the vibrational levels; and f_{transl} denotes the partition function of the translational levels belonging to Class B and measured from the energy level of the convergence limit taken as a zero.

If we confine our attention to the molecules for which the center of gravity of the bond in question is restricted to some segment ds along the direction of the bond,¹⁸ then the partition function f_{transl} may be represented, with a fair degree of accuracy, as a translational partition function of "a particle in a box", i.e.:

$$f_{\text{transl}} = (2\pi\mu kT)^{1/2} \cdot h^{-1} ds$$

¹⁸ We assume the origin of the coördinates to be fixed at one end of the bond in question.

The fraction of the molecules which can decompose by the rupture of the bond in question (i.e., which contain the requisite amount of energy in the bond to be broken) and for which the center of gravity of this bond is confined to the segment ds is given by:

$$\frac{\text{Number of molecules which can decompose}}{\text{Total number of molecules}} =$$

$$= \frac{(\pi' f_i) \cdot e^{-D/kT} \cdot (2\pi\mu kT)^{1/2} \cdot h^{-1} \cdot ds}{(\pi' f_i) \cdot (\sum e^{-\epsilon_j/kT} + e^{-D/kT} \cdot f_{trans})} \approx \\ \approx \frac{e^{-D/kT} \cdot (2\pi\mu kT)^{1/2} \cdot h^{-1} \cdot ds}{\sum e^{-\epsilon_j/kT}}$$

This expression can be further simplified if we assume that the energy levels ϵ_j correspond to a harmonic oscillator so that

$$\sum e^{-\epsilon_j/kT} = 1 + e^{-h\nu_0/kT} + e^{-2h\nu_0/kT} + e^{-3h\nu_0/kT} + \dots \\ = (1 - e^{-h\nu_0/kT})^{-1}$$

where ν_0 denotes the fundamental vibration of the bond in question. We arrive, therefore, at the expression:

$$\frac{\text{Number of molecules which may decompose}}{\text{Total number of molecules}} =$$

$$= (2\pi\mu kT)^{1/2} \cdot (1 - e^{-h\nu_0/kT}) \cdot h^{-1} \cdot e^{-D/kT} \cdot ds$$

We can now assume that half of the molecules which can decompose (and for which the center of gravity is confined to the segment ds) are moving in the direction of decomposition with an average thermal velocity $(2kT/\pi\mu)^{1/2}$. The rate of decomposition is given, therefore, by the number of these molecules for which the center of gravity will pass the segment ds in a unit of time, i.e.:

$$\text{Rate constant of decomposition} = \frac{\frac{1}{2}(2\pi\mu kT)^{1/2} \cdot (1 - e^{-h\nu_0/kT}) \cdot h^{-1} \cdot e^{-D/kT} \cdot ds}{(2kT/\pi\mu)^{-1/2} \cdot ds}$$

$$k = \text{rate constant of decomposition} = (kT/h)(1 - e^{-h\nu_0/kT}) \cdot e^{-D/kT}$$

We have to distinguish between two extreme cases:

$$\text{A. } h\nu_0 \ll kT$$

$$\text{B. } h\nu_0 \gg kT$$

$$\text{Assumption A: } h\nu_0 \ll kT$$

In case A

$$(1 - e^{-h\nu_0/kT}) \approx h\nu_0/kT$$

and the expression for the rate constant is reduced to

$$k = \text{rate constant of decomposition} = \nu_0 \cdot e^{-D/kT}$$

This case, which was discussed by M. G. Evans and G. S. Rushbrooke (55), gives the correct results for either a very high temperature or very "soft" bonds.

It is necessary to analyze further the implications of the formula derived above for the rate constant of a unimolecular dissociation. We notice, first of all, that the nonexponential term is a constant which is truly temperature independent, and therefore

$$RT^2 \cdot \frac{d \ln k}{dT} = \frac{D}{kT^2} \cdot RT^2 = ND$$

where N = Avogadro's number. As the left-hand side is the Arrhenius activation energy (sometimes called "experimental activation energy"), we have shown that if assumption A is valid then the experimental activation energy of a unimolecular dissociation process in which one bond is ruptured is *exactly* equal to the dissociation energy of this bond. This provides a justification for the kinetic method of determining the bond dissociation energy.

Before we continue this discussion there are some apparent contradictions to be elucidated. It is known that for any reversible reaction



the heat of reaction is given by the difference between the activation energies of the forward and back reactions:

$$\Delta E = E_1 - E_2^{19}$$

We assume that the recombination of radicals does not involve an activation energy, and we might conclude, therefore, that the activation energy of the dissociation process is equal to the heat of reaction:

$$\Delta E = E_1 \quad (E_2 = 0)$$

The heat of reaction at temperature T is of course different from the heat of reaction at 0°K., and thus we arrive at the conclusion:

$$\Delta E \neq \Delta E^0 = D$$

i.e.,

$$E_1 \neq D$$

which seems to contradict the previous statement.

In order to clarify this point we must note that E_1 and E_2 in the expression $\Delta E = E_1 - E_2$ have the meaning of "experimental activation energies," i.e., each of these activations can be represented by an expression of the type $RT^2 \cdot d \ln k/dT$. It was shown previously that for unimolecular dissociations:

$$RT^2 \cdot d \ln k_1/dT = E_1 = D = \Delta E^0$$

In order to find $RT^2 \cdot d \ln k_2/dT$ we write:

$$K_{eq} = \frac{k_1}{k_2} = \frac{f_{final}}{f_{initial}} \cdot e^{-\Delta E^0/RT}$$

¹⁹ The heat of reaction is measured here at constant volume.

K_{eq} = the equilibrium constant for $A \rightleftharpoons B + C$; f_{final} and $f_{initial}$ are the partition functions of products B and C, and of reagent A, respectively. Hence:

$$k_2 = \frac{f_{initial}}{f_{final}} \cdot e^{+\Delta E^0/RT} \cdot \nu_0 \cdot e^{-D/RT}$$

and because $\Delta E^0 = D$, we obtain:

$$RT^2 \cdot \frac{d \ln k_2}{dT} = RT^2 \frac{d(\ln f_{initial})}{dT} - RT^2 \frac{d(\ln f_{final})}{dT}$$

The left-hand side of this expression gives E_2 , while the right-hand side gives $\Delta E^0 - \Delta E$. We see, therefore, that although there is no potential energy barrier

TABLE 7

Frequency factors for various unimolecular dissociation processes in which one bond is ruptured

PROCESS	<i>E</i> kcal./mole	<i>μ</i>
		sec. ⁻¹
$C_6H_5CH_3 \rightarrow C_6H_5CH_2 + H$	77.5	$3 \times 0.7 \times 10^{12}$
$m\text{-CH}_2C_6H_4CH_3 \rightarrow m\text{-CH}_2C_6H_4CH_2 + H$	77.5	$6 \times 0.7 \times 10^{12}$
$p\text{-CH}_2C_6H_4CH_3 \rightarrow p\text{-CH}_2C_6H_4CH_2 + H$	76	$6 \times 0.8 \times 10^{12}$
$\alpha\text{-CH}_2C_6H_4CH_3 \rightarrow \alpha\text{-CH}_2C_6H_4CH_2 + H$	75	$6 \times 0.8 \times 10^{12}$
$C_6H_5CH_2Br \rightarrow C_6H_5CH_2 + Br$	50.5	1×10^{13}
$C_6H_5CH_2CH_3 \rightarrow C_6H_5CH_2 + CH_3$	63	1×10^{13}
$C_6H_5CH_2NH_2 \rightarrow C_6H_5CH_2 + NH_2$	59	6×10^{12}
$C_6H_5CH_2COCH_3 \rightarrow C_6H_5CH_2 + COCH_3$	63	8×10^{12}
$N_2H_4 \rightarrow 2NH_2$	60	4×10^{12}
$CH_3COCOCH_3 \rightarrow 2CH_3CO$	60	6×10^{12}
$(CH_3)_3COOC(CH_3)_3 \rightarrow 2(CH_3)_3CO$	34	2×10^{12}
$CH_2=CHCH_2Br \rightarrow CH_2=CHCH_2 + Br$	47.5	5×10^{12}
$(C_6H_5)_3CC(C_6H_5)_3 \rightarrow 2(C_6H_5)_3C$	11	5×10^{12}
$(C_6H_5CO)OO(COC_6H_5) \rightarrow 2C_6H_5COO$	27-33	$10^{12}-10^{14}$
$(CH_3CO)OO(COCH_3) \rightarrow 2CH_3COO$	31	8×10^{14}
$C_2H_5OOC_2H_5 \rightarrow 2C_2H_5O$	31	5×10^{14}

for the recombination, there is an "experimental activation energy" which just accounts for the difference between D and ΔE . At 0°K. we get, of course:

$$\Delta E^0 = E_1 - 0 = D$$

The expression derived here for the rate constant of unimolecular dissociation demands that the frequency factor should be nearly equal to the fundamental vibration frequency of the bond in question. It is possible, therefore, to check the theory by comparing frequency factors determined experimentally with the corresponding vibrational frequencies. Table 7 lists the frequency factors obtained for various unimolecular dissociation processes in which one bond is ruptured. One observes that their orders of magnitude are $10^{12}-10^{14}$ sec.⁻¹. On the other hand, the corresponding fundamental vibrational frequencies are of the order of $10^{13}-10^{14}$ sec.⁻¹; hence the agreement appears to be reasonable. It seems,

on the whole, that the frequency factors are lower by about a factor of 10 than the fundamental frequencies; this may indicate that in the activated complex that part of the molecule which is not involved in the decomposition is less flexible than it is in "normal" molecules.

$$\text{Assumption B: } h\nu_0 \gg kT$$

In case B

$$(1 - e^{-h\nu_0/kT}) \approx 1$$

and the expression for the rate constant is reduced to

$$k = \text{rate constant of decomposition} = \frac{kT}{h} \cdot e^{-D/kT}$$

The "experimental" activation energy measured by $RT^2 d \ln k/dT$ is given now by

$$E_{\text{exp}} = RT + D$$

We conclude, therefore, that at the temperature of about 1000°K. the "experimental" activation energy gives results which are too high by about 2 kcal./mole. The "experimental" frequency factor obtained from the expression $k = v_{\text{exp}} \cdot \exp(-E_{\text{exp}}/RT)$ should be greater than $kT/h \approx 10^{13}$ by about a factor of 3. It seems again that the theory predicts slightly higher values for v_{exp} , than are actually observed.

We arrive thus at the conclusion that the "experimental" activation energies yield values which are within $D + 2 > E_{\text{exp}} > D$. If $h\nu_0/kT$ is of the order of 1, the E_{exp} approximates closer to D than in case B. The same effect is caused by the anharmonicity of vibration; it makes $kT/h \cdot f$, less dependent on temperature and decreases the difference between E_{exp} and D .

Finally we have to consider the influence of the term f^t/f_{in} (excluding the partition function linked with the bond to be broken). If the transition state is "softer" than the initial state, then the frequency factor contains an additional term increasing with temperature in the denominator. That helps to make the frequency factor temperature independent and approximates E_{exp} to D . On the other hand, the contrary is true if the transition state is "harder" than the initial state.

It seems adequate to summarize this discussion with the statement:

The experimental activation energy defined by the expression $RT^2 d \ln k/dT$ gives a fair approximation to the bond dissociation energy, particularly if the experimental frequency factor is close to $10^{13} \text{ sec.}^{-1}$

E. Experimental problems in the determination of the rate of initial decomposition

Let us consider now the conditions which enable one to measure the rate of the primary unimolecular dissociation $\text{RR}' \rightarrow \text{R} + \text{R}'$. The experimentation is limited, of course, to the type of decomposition in which the weakest bond of the molecule is ruptured, and it is desirable, therefore, that this bond should be considerably weaker than any other bond in the molecule.

The primary dissociation process is followed by the subsequent reactions of the radicals formed, and consequently the investigator is confronted with the possibility of numerous complications which may obscure the kinetics of the decomposition and make their interpretation ambiguous. A straightforward approach would be one based on a direct measurement of the rate of formation of the radicals produced initially. This, however, cannot be achieved by simply estimating the concentration of radicals present in the system. As soon as the radicals are produced by decomposition, they begin to react either with each other or with other surrounding molecules. The measured concentration of radicals, therefore, corresponds to their *stationary* concentration and since this is not proportional to the time of reaction it cannot measure the rate of the dissociation process.

It seems probable that in a flow system in which the reactants pass very rapidly through the furnace, i.e., when the time of contact is extremely short, the radicals produced will have no chance of recombining or reacting in any way. If, in a case like this, one were to count them on their leaving the reaction vessel one would be able to measure the rate of dissociation (per cent of decomposed molecules divided by time of contact). This idea was developed by F. O. Rice and his collaborators and is discussed more fully in Section IV,F (page 118).

An interesting case is encountered when nearly all the radicals produced are removed by their mutual recombination. Such a system approximates closely to the equilibrium state $R'R'' \rightleftharpoons R' + R''$. Hence, when a minute quantity of these radicals is removed by some *irreversible* process which produces molecules X, then the rate of formation of X depends on the equilibrium concentration of the radicals. The overall activation energy, corresponding to the process of X formation, involves, therefore, the activation energy of the reaction $R \rightarrow X$ (whatever its mechanism may be) and the heat of dissociation of $R'\cdot R''$. If the former is known, or can be independently estimated, then the heat of dissociation of $R'\cdot R''$ can be computed from the overall activation energy of X formation. This is the basis of a combined equilibrium and kinetic method, illustrated by the example given on page 127.

The estimation of the rate of initial dissociation is accomplished most satisfactorily in a system in which the radicals are removed as soon as they are formed, without regenerating the original molecules. In such a system we avoid any complications caused by the back reaction and the rate of formation of the final product from the primary radicals measures the rate of initial dissociation. However, since all reactions between radicals and molecules must produce radicals, there is a danger of starting a chain reaction. It is possible, in principle, to obtain the required information even by investigating a chain reaction, since the determination of both the length of the chain and the overall rate of chain reaction would enable us to compute the rate of initiation. In practice, however, the kinetics of chain reactions is very ambiguous and, in the writer's opinion, these reactions are not to be recommended for the estimation of the rate of initial dissociation.²⁰

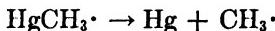
²⁰ See, for example, page 132.

There are two cases in which the chain reaction might be prevented:

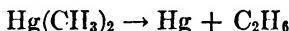
(1) When the radicals are removed rapidly by a recombination which does not produce the original molecules. Such a process generally requires two stages: e.g., the initial decomposition of mercury dimethyl takes place according to the equation



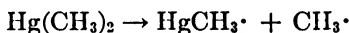
and it is followed by rapid decomposition of $\text{HgCH}_3\cdot$.



Thus, the recombination of $\text{HgCH}_3\cdot$ and $\text{CH}_3\cdot$ radicals into the original molecules of mercury dimethyl is prevented. Now suppose that the recombination of methyl radicals into ethane molecules is the most effective reaction by which methyl radicals are removed from the system. In this case, the overall process is represented by the equation:



and will be governed, kinetically, by the unimolecular rate-determining dissociation:²¹



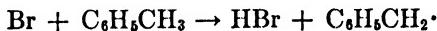
(2) When radicals initially formed are rapidly removed by some reactions. These eventually produce *stable* radicals which neither decompose into simpler fragments nor react with molecules present in the system. This is illustrated by two examples:

Example 1:

Decomposition of benzyl bromide produces reactive bromine atoms and relatively inert benzyl radicals:



If this reaction is carried out in an excess of toluene, then reactive bromine atoms are removed rapidly by the interaction with $\text{C}_6\text{H}_5\text{CH}_3$:



producing inert benzyl radicals. The benzyl radicals may be continuously removed from the reaction vessel and they dimerize eventually in the outlet tube. The rate of the initial dissociation can be measured, therefore, by the rate of formation of either hydrogen bromide or bibenzyl.²²

²¹ A detailed discussion of this decomposition, investigated by E. Warhurst and G. B. Gowenlock, is reported on page 151.

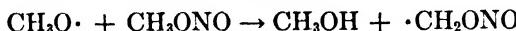
²² Decompositions of this type are discussed on page 136.

Example 2:

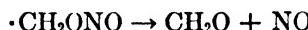
Primary decomposition of methyl nitrite takes place according to the equation:



The reactive $\text{CH}_3\text{O}\cdot$ radical interacts with a molecule of undecomposed nitrite and produces the unstable radical $\cdot\text{CH}_2\text{ONO}$:



Finally, the unstable $\cdot\text{CH}_2\text{ONO}$ radical decomposes and a stable NO radical is produced:



According to this mechanism the rate of initial decomposition may be measured by the rate of formation of nitric oxide.²³

F. The determination of bond dissociation energy by the mirror technique

It was first demonstrated by F. Paneth and his collaborators (129, 130) that free methyl and ethyl radicals may exist in the gas phase. They have shown that these radicals reacted easily with metallic mirrors deposited on the walls of the tube, and the reciprocal of the time of removal of a "standard" mirror was taken as a measure of their "activities", i.e., an entity proportional to their concentration.

The mirror technique was further developed and improved by F. O. Rice and his colleagues (146, 147), who succeeded in demonstrating the presence of free methyl radicals amongst the products of decomposition of various organic compounds. Having proved that under their experimental conditions most compounds appeared to decompose homogeneously and according to a unimolecular law and that these decompositions involved a primary splitting of the molecule into two radicals, they deduced that the activation energies of these decompositions should measure the dissociation energies of the relevant bonds. It was further assumed that for small fractional decompositions the concentration of radicals at the end of the furnace is proportional to the rate of dissociation of an organic compound. This assumption may be sound if the recombination of radicals is negligible, as would be the case for low pressures and extremely short times of contact.

In the actual experimental set-up the vapor of an organic compound was passed rapidly through a silica tube, which was heated by means of an electric furnace to a temperature at which slight decomposition took place. The pressure was kept low (0.2–2 mm. of mercury) and the time of contact was very short, being of the order of 0.001 sec. Standard mirrors of antimony were placed at varying distances from the end of the furnace and the times of their removal were determined for each position. The time of removal of a mirror at the end of the

²³ Decompositions of organic nitrates are discussed on page 141.

furnace was computed by extrapolation.²⁴ By this method the relative concentrations of radicals at the end of the furnace were determined for various temperatures of the decomposition and these data were used for the computation of the required activation energy (145).

F. O. Rice and W. R. Johnston (145) have discussed various objections which could be urged against this method of determining the activation energy. They argued, firstly, that the radicals originally formed undoubtedly decompose further and that, therefore, the activation energy of this process would be measured simultaneously; secondly, that the free radicals reacting with the surrounding molecules might start a chain reaction; and, thirdly, that, since the organic vapor passes through the furnace in about 0.001 sec., it is doubtful whether it reaches the temperature registered by the thermocouple.

With regard to the first of these objections, Rice and Johnston argued that the decomposition of the larger radicals into olefin molecules and methyl radicals has an activation energy of 40–60 kcal./mole lower than that of the initial dissociation of the parent compound. This is in their opinion due to the formation of a double bond, which takes place simultaneously with the dissociation process of the complex radical. The rate of formation of methyl radicals should, therefore, be equal to the rate of formation of the primary complex radicals and the activation energy measured should correspond to that of the primary dissociation process.

The second objection Rice and Johnston consider to be nonessential. Even if a chain process ensued, it would have no effect on the experimental measurements, since a reaction between a radical and molecule must of necessity lead to the formation of another radical. The chain termination seems to be negligible, because of the extremely short time of contact and low pressure.

Finally, the last objection was refuted by showing that changing of the diameter and length of the reaction vessel, as well as the rate of flow, had no appreciable effect on the final results. Similarly, no effect was observed when a preheater was fitted to the reaction vessel immediately in front of the main furnace. Moreover, the theoretical treatment of these problems by Herzfeld (80) seems to confirm fully the conclusion drawn from the experimental evidence above.

However, the following objection was not considered by Rice: The time of removal of a mirror at the end of the furnace was computed by extrapolation, the necessary data being provided by determining the times of the removal of mirrors placed at various distances from the furnace along the *cold* tube. The decay of radicals in the cold tube was quite different from the decay in the hot zone immediately following the end of the furnace. It is doubtful, therefore, if the extrapolated time of removal was correct. Moreover, the variation of the temperature of the furnace was changing both the temperature distribution and the length of the hot zone. This effect might systematically alter the error involved in the extrapolation yielding the time of the removal of the mirror at the end of the furnace. Any variation of the error with the temperature causes,

²⁴ A direct determination of this time would have been prevented by the sublimation of the mirror, were it deposited on the hot tube in the vicinity of the furnace.

of course, an appreciable error in the estimation of the temperature coefficient of the activity, i.e., in the activation energy determined. We doubt whether this objection could be refuted merely by the fact that variation of rate of flow did not produce a greater change in activation energy than ± 3 kcal./mole, which Rice considered as the experimental error of his determinations.²⁵

The difficulties of the extrapolation discussed above were strongly emphasized by J. S. A. Forsyth (57). This worker has shown that nitric oxide apparently did not inhibit the reaction of methyl radicals at distances shorter than 4 cm. from the end of the furnace. He concluded that the gas leaving the furnace is still hot enough to decompose and to generate further quantities of radicals

TABLE 8
Bond dissociation energies estimated by mirror technique

COMPOUND	FURNACE TEMPERATURE	E
		°K.
CH ₃ —CH ₃	1179, 1233	79.5
CH ₃ OCO—OCH ₃ (?)	1043, 1080, 1152, 1188	74.2
CH ₃ CH ₂ —CH ₃	1010, 1080, 1152	71.5
n-C ₄ H ₁₀	1010, 1080, 1152	65.4
n-C ₄ H ₁₂	996, 1033, 1052, 1080	64.0
n-C ₇ H ₁₆	1010, 1080	63.2
CH ₃ CO—CH ₃	1010, 1080, 1134	70.9
CH ₃ CO—H (?)	1116, 1152, 1179	69.4
CH ₃ —CH ₂ OH	1134, 1152, 1223	68.6
CH ₃ O—CH ₃	1080, 1152, 1188	81.1
C ₂ H ₅ OC ₂ H ₅	1010, 1080, 1152	68.6
CH ₃ —CH ₂	1052, 1088, 1134, 1188	44.0
\ \ \ O		
(CH ₃) ₂ N—CH ₃	953, 1010, 1080	50.8
CH ₃ NH—CH ₃	1080, 1116, 1152, 1188	52.0

even at some distance from the furnace. He suggested that the "effective" end of the furnace should be taken as 4 cm. from its actual end.

To illustrate the application of the mirror technique we reproduce here table 8, taken from the paper by Rice and Johnston. These workers also showed their results by giving the plots of log of "activity" (i.e., time of removal of a mirror at the end of a furnace) against $1/T$, which gave excellent straight lines over a range of 150°C.

Consideration of table 8 leads to the following conclusions: In the first place, all the activation energies quoted seem to be definitely smaller than the relevant bond dissociation energies, taking for the latter values which are now considered to be the best. In the writer's opinion, this general trend may be attributed to errors in the extrapolated time of removal of the mirror at the end of the fur-

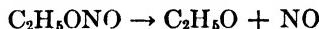
²⁵ In Steacie's opinion, the experimental error in determining activation energies by the mirror technique may be as high as ± 10 kcal./mole.

nace. The hot zone following the reaction vessel is longer and hotter the higher the furnace temperature. Therefore the concentration of radicals in the region of mirror deposition corresponds to a smaller fraction of their initial concentration²⁶ the higher the temperature of the furnace. Consequently, the apparent activation energy is lower than the "true" activation energy.

The gradation of results presented in table 8 seems to be reasonable. We notice a decrease in activation energies in the series C_2H_6 , C_3H_8 , $n-C_4H_{10}$, $n-C_5H_{12}$, and $n-C_7H_{16}$, although the recorded differences seem greater than would be expected, e.g., the difference between $D(CH_3—CH_3)$ and $D(C_2H_6—CH_3)$ is probably considerably smaller than the 8 kcal./mole reported. The results obtained for $n-C_4H_{10}$, $n-C_5H_{12}$, and $n-C_7H_{16}$ leave us unable to decide which was the bond initially broken. Similarly, it is impossible to say whether the decomposition of dimethyl carbonate takes place at $CH_3OCO—OCH_3$ or at $CH_3OCOO—CH_3$, and whether, in the decomposition of acetaldehyde, the C—C or the C—H bond is primarily broken. It is interesting to note that the results obtained for dimethyl ether indicate that the dissociation energy of a C—O bond is greater than the dissociation energy of a C—C bond, a conclusion which is in accord with our present views. The difference in activation energies obtained for dimethyl ether and diethyl ether seems to indicate that, in the latter case, a C—C bond is broken and not a C—O bond. Finally, one notes that the activation energies obtained for amines are exceptionally low. The writer believes that $D[(CH_3)_2N—CH_3]$ and $D(CH_3NH—CH_3)$ are much higher, probably of the order of 70–75 kcal./mole.

The mirror technique was used by Rice and his colleagues in several other cases. F. O. Rice and M. D. Dooley (143) used this technique for determining $D(CH_3—H)$. They proved that under their experimental conditions CH_4 decomposes into $CH_3 + H$, and estimated the activation energy at 100 ± 6 kcal./mole; this result is in excellent agreement with the value of 101 kcal./mole for $D(CH_3—H)$ at present accepted as the most reliable. The same authors reinvestigated the thermal decomposition of ethane, demonstrated the formation of methyl radicals, and estimated the activation energy at 79.5 ± 3 kcal./mole (144).

The decomposition of ethyl nitrite was investigated by the mirror technique by F. O. Rice and E. L. Rodowskas (148). The activation energy of the process:



was estimated by them at 35 ± 3 kcal./mole (see also page 143).

We conclude that the mirror technique is an extremely sensitive tool for the detection of radicals. We do not think, however, that it can be accurate enough for the estimation of bond dissociation energies. The method is based on a calculation of the thermal coefficient of the rate constant and, as shown in Section IV,A, such a calculation is susceptible to errors resulting from the occurrence of various side reactions. The mirror technique fails to eliminate the

²⁶ By "initial concentration of the radicals" is meant the concentration of radicals at the end of the furnace.

occurrence of possible side reactions and the time lag between the end of the reaction (products leave the furnace) and the actual measurements (products arrive at the mirror) is a source of appreciable errors which, in the writer's opinion, tend to decrease the observed activation energy. Perhaps the time lag could be eliminated by using the mass-spectroscopic technique described by G. C. Eltenton (52). The radicals produced in the reaction vessel leak through a small orifice directly into the ionizing chamber, where their presence can be detected in the usual way, since the ionization potential required for formation of the relevant ion from the radical is much lower than that required for formation of the same ion from the molecule.

G. The determination of the C—I bond dissociation energy in organic iodides

The C—I bond dissociation energy of various organic iodides was estimated by E. T. Butler and M. Polanyi (35) and by E. T. Butler, E. Mandel, and M. Polanyi (33), who investigated the rate of pyrolysis of a series of organic iodides by a flow technique. They measured the fraction of iodide decomposed by the amounts of free iodine formed in the reaction. In their opinion the use of a flow technique was advantageous, since the accumulation of the products resulting from an extended period of flow made it possible (a) to work with a very small partial pressure of organic substance and (b) to limit the total decomposition to a very small percentage. Thus, by maintaining low concentrations of the initial and final products, the chances of secondary reactions were considerably reduced. These were further suppressed by the brief duration of the reaction, which was over in a second or less as the gases passed through the reaction vessel.

Since the C—I bond is the weakest bond in organic iodides, it is obvious that the first step in the pyrolysis of these compounds involves the rupture of this bond in preference to any other:



The formation of free iodine must be attributed to this reaction.²⁷

Neither the radicals R nor the iodine atoms can be the final products of the decomposition. The appearance of I₂ suggests the reaction:



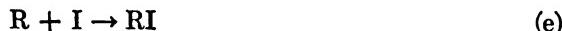
and this can take place either in the gas phase, by three-body collisions, or on the walls of the reaction vessel. Whether reaction c occurs in the reaction vessel itself, or in the tubes leading to the trap in which iodine is condensed has been left open. Radicals R must also be removed from the system by some secondary reactions which can be represented by the general equation:



²⁷ The experiments of Butler and Polanyi demonstrated that pyrolysis of many iodides produced hydrogen iodide in addition to free iodine. They explained the formation of hydrogen iodide by assuming an alternative unimolecular decomposition of the type:



If reaction c is the only one which consumes iodine atoms, i.e., if the back reactions e and f



can be neglected, and if the radicals R are removed from the system without initiating any chain decomposition of RI, then the rate of formation of iodine molecules measures the rate of the initial decomposition (equation a).

Butler and Polanyi tried to obtain further evidence for the occurrence and extent of back reactions e and f in the following ways:

(a) In some experiments mercury vapor, or nitric oxide, was admitted to the system. It is known that mercury vapor reacts readily with iodine atoms or iodine molecules (123) removing them from the system, while nitric oxide is well known for its readiness to combine with radicals (167); therefore, it was reasonable to assume that either of these substances must suppress the back reactions e and f. Actually, they found that admission of mercury vapor to ethyl iodide had no effect on the rate of decomposition, while admission of nitric oxide doubled the rate of decomposition, thus indicating only 50 per cent of back reaction.

(b) If the back reaction were only a minor disturbing factor, and if the initial decomposition were the actual rate-determining step, then the activation energies derived from the temperature coefficient of the rate constant would agree closely with the activation energy derived on the assumption of the frequency factor being 10^{13} sec.⁻¹ (see Section IV,B for details of the computation). On the other hand, if the back reactions were very fast, then the latter computation would yield a much higher value of the apparent activation energy. In fact, Butler and Polanyi found that for the decomposition of *n*-propyl iodide and *n*-butyl iodide the activation energies calculated from the temperature coefficients were 52 kcal./mole and 53 kcal./mole, respectively, whereas the activation energies computed on the basis of an assumed frequency factor at 10^{13} sec.⁻¹ came out at 50 kcal./mole and 49 kcal./mole, respectively.

On the basis of these two arguments Butler and Polanyi concluded that the rate of formation of iodine molecules approximates closely to the rate of initial decomposition of RI. They were aware, of course, of the fact that the main reaction was accompanied by various complicating reactions which made this approximation rather crude.²⁸ Therefore they did not consider the activation energies calculated from the temperature coefficient of the rate constant to be reliable. They were convinced, however, that no great error was introduced by calculating the activation energy of the primary process by the method in which the frequency factor was assumed at 10^{13} sec.⁻¹, particularly if the data used for these computations were taken from experiments performed at the lowest temperatures and with the shortest times of contact (cf. Section IV,B).

²⁸ The fact that the calculated unimolecular rate "constant" varied with changes in the time of contact, pressure, etc. demonstrated clearly that the decomposition is not a simple unimolecular reaction.

In consequence, the activation energies were computed in this way and identified with the relevant C—I bond dissociation energies. The results are given in table 9, taken from the original papers of Polanyi *et al.* The third column of table 9 gives the C—I bond dissociation energies which in the writer's opinion are more reliable, being computed on the basis of more recent evidence. Comparison of the results listed in columns 2 and 3 demonstrates that in many instances the original values of Butler and Polanyi are sound.

We shall now examine more closely the assumptions made by Butler and Polanyi. Intrinsically there is no reason to assume that the combination of iodine

TABLE 9
C—I bond dissociation energies

COMPOUND	<i>D</i> (C—I) (BUTLER AND POLANYI)	<i>D</i> (C—I) MOST RELIABLE VALUES AT PRESENT	
		Kilocalories per mole	References
CH ₃ —I	kcal./mole (54)	54-55	(36, 206)
C ₂ H ₅ —I	52	51-53	(182)
<i>n</i> -C ₃ H ₇ —I	50		
Iso-C ₂ H ₅ —I	46		
<i>n</i> -C ₄ H ₉ —I	49		
<i>tert</i> -C ₄ H ₉ —I	45		
(CH ₂ =CHCH ₂)—I	39	~34	(61, 163)
(CH ₂ =CH)—I	55		
C ₆ H ₅ CH ₂ —I	44	~37	(61, 182)
C ₆ H ₅ —I	54		
CH ₃ CO—I	(51)	~41-46	(37, 195)
C ₆ H ₅ CO—I	44		
CH ₃ COCH ₃ —I	45		
Cyclo-C ₆ H ₁₁ —I	49		
C ₆ H ₅ CH ₂ CH ₂ —I	50		
CHCl ₂ —I	42		
CHBr ₂ —I	41		
CH ₂ ClCH ₂ —I	46		

atoms to iodine molecules is more likely than the recombination of iodine atoms with R radicals. The mutual combination of iodine atoms *must* take place by a three-body collision if it occurs in the gas phase. On the other hand, if the dissociation process RI → R + I is truly unimolecular (as was assumed by Butler and Polanyi), then the recombination R + I → RI has to be a truly bimolecular process (under the experimental conditions which prevailed in the dissociation process). It follows, therefore, that R + I → RI is more likely to occur than I + I + M → I₂ + M. The chances of recombination are further increased by the reaction:



It is known that iodine molecules react readily with radicals, and since the concentration of I₂ increases during the actual dissociation process, reaction f

should be favored by a greater extent of decomposition. For example, a longer time of contact or a higher temperature of pyrolysis should increase back reaction f , and an examination of the data reported by Butler and Polanyi reveals indeed a decrease of the unimolecular rate "constant" with increasing time of contact. Besides, in some instances the apparent activation energy, calculated from the temperature coefficient of the rate constant, is too low, thus indicating a more efficient back reaction at higher temperature.

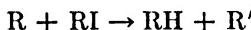
These arguments convince us that the back reaction cannot be prevented, at least efficiently enough, by the combination of iodine atoms to iodine molecules. However, Butler and Polanyi accumulated considerable evidence which pointed to the fact that in the pyrolyses of ethyl, propyl, and *n*-butyl iodides the back reaction was negligible. We conclude, therefore, that in the pyrolyses of these compounds the back reaction is prevented by a rapid removal of organic radicals R from the system.

There are two types of reactions which may remove radicals R from the system:



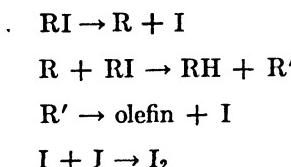
where R' represents a radical of the type $\cdot\text{CH}_2\text{CH}_2\text{I}$. The efficiency of reactions of type I cannot be greater than the efficiency of the back reactions $R + I \rightarrow RI$ or $R + I_2 \rightarrow RI + I$. On the other hand, the efficiency of the reaction of type II might be greater, owing to a much higher concentration of RI as compared with the concentration of R.

There is additional evidence in favor of the assumed reaction:



The photochemical investigations by W. West and E. Ginsburg (214) and by W. West and L. Schlessinger (215) clearly demonstrated that at room temperature the back reaction, i.e., the re-formation of RI, was very efficient (the presence of a silver foil in the reaction vessel increased the rate of photolysis by a factor of 10 to 30). This means then that the reaction which removes the radicals has an activation energy, thus being efficient at high temperatures of pyrolysis and of little importance at low temperatures of photolysis. It is unlikely that the dimerization or disproportionation of radicals requires any appreciable activation energy (both being highly exothermic reactions), but it is plausible to attribute an activation energy to the reaction $R + RI \rightarrow RH + R'$.

The mechanism of pyrolysis of organic iodides, therefore, takes the following shape:

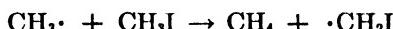


The third reaction of this scheme is extremely plausible, as the C—I bond dissociation energy in the radical R' (e.g., ·CH₂CH₂I) is considerably lower than D(R—I). An examination of the above scheme shows that it would lead to first-order kinetics, the unimolecular dissociation of RI being the rate-determining step. Two iodine atoms would be formed for every molecule of RI primarily decomposed.

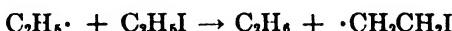
It is the belief of the writer that the pyrolysis of ethyl, *n*-propyl, and *n*-butyl iodides approximates to this scheme. The unimolecular rate constants for *n*-propyl iodide and *n*-butyl iodide reported in table 1 of Butler and Polanyi's paper did not vary appreciably with changes of partial pressure of iodide and with different times of contact. The experimental frequency factors came close to the theoretically required value of 10¹³ sec.⁻¹ Similar conclusions might be drawn from the results of the pyrolysis of ethyl iodide, reinvestigated in Polanyi's laboratory by G. B. Gowenlock (68) and by M. Szwarc (182). The experimental activation energy calculated from the temperature coefficient of the rate constant was estimated at 54 kcal./mole by Szwarc and 55–56 kcal./mole by Gowenlock. The activation energy computed on the basis of frequency factors, assumed at 10¹³ sec.⁻¹, was 51–52 kcal./mole. This value agrees well with the D(C₂H₅—I) estimated thermochemically at 51 kcal./mole. Nevertheless, closer analysis of the kinetics of these pyrolyses shows that various other processes participate to some extent in the overall decomposition and, notwithstanding all this extensive work, it has been impossible to elucidate finally the details of these reactions.

The kinetics of the pyrolysis of other iodides was much more complicated than those observed for ethyl, *n*-propyl, and *n*-butyl iodides. To illustrate the various complicating factors we shall discuss the pyrolyses of methyl iodide, benzyl iodide, and allyl iodide.

Reinvestigation of the pyrolysis of methyl iodide (182) demonstrated that the formation of iodine molecules was accompanied by the formation of methane. The rate of decomposition was much lower than expected, and it obeyed kinetics of an order higher than 1. It seems that the back reaction was much more efficient in this decomposition, indicating a higher activation energy for the reaction:

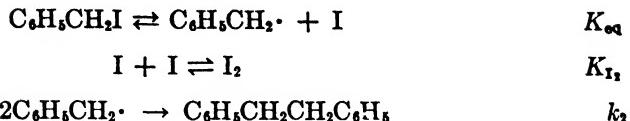


than for the reaction:



The formation of the radical ·CH₂I is a further complicating factor. While a ·CH₂CH₂I radical decomposes easily into an iodine atom and an ethylene molecule, the ·CH₂I radical decomposes probably more slowly and then forms another radical, i.e., CH₂. It seems also that some steps of the decomposition of methyl iodide involve a heterogeneous wall reaction.

Reinvestigation of the pyrolysis of benzyl iodide (182) led to the postulation of the following mechanism:



The benzyl radicals appeared very unreactive. They were not removed by the reaction $\text{R} + \text{RI} \rightarrow \text{RH} + \text{R}'$, and therefore the system approached an equilibrium state for R , I , and I_2 . Consequently, the dimerization of benzyl radicals was the rate-determining step. For low temperatures and very small percentages of decomposition it was found that the unimolecular rate constant was inversely proportional to the square root of the time of contact. Denoting by X the amount of I_2 formed and by C the initial concentration of benzyl iodide (which we can regard as constant for very low percentages of decomposition) we derive the following expression:

$$\begin{aligned} [\text{I}] &= (K_{\text{I}_2}\cdot X)^{1/2} & ([\text{I}_2] &= X) \\ [\text{C}_6\text{H}_5\text{CH}_2\cdot] &= K_{\text{eq}} \cdot C / [\text{I}] = K_{\text{eq}} \cdot C / K_{\text{I}_2}\cdot X^{1/2} \\ \frac{1}{2} \cdot \frac{dX}{dt} &= k'_2 [\text{C}_6\text{H}_5\text{CH}_2\cdot]^2 = \frac{k_2 \cdot K_{\text{eq}}^2}{K_{\text{I}_2}} \cdot \frac{C^2}{X} \end{aligned}$$

and on integration we obtain:

$$\begin{aligned} \frac{1}{4}X^2 &= (k_2 \cdot K_{\text{eq}}^2 / K_{\text{I}_2}) = C^2 t \\ \frac{X^2}{t^2 C^2} &= \text{const. } \frac{1}{t} \end{aligned}$$

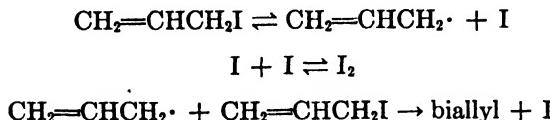
where

$$\text{const. } \frac{4k_2 \cdot K_{\text{eq}}^2}{K_{\text{I}_2}}$$

As the left-hand side is the square of the unimolecular rate constant we have derived the above empirical relationship: the unimolecular rate constant is inversely proportional to the square root of the time of contact.

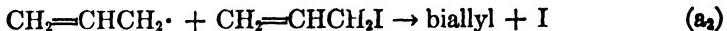
The scheme discussed above represents only the first approximation of the actual decomposition of benzyl iodide. The participation of other complicating factors prevented the determination of the C—I bond dissociation energy in this compound.

The pyrolysis of allyl iodide was reinvestigated in a static system (163). It would appear that the following scheme represents the best first approximation to the actual reaction:



The kinetic evidence favors the last reaction rather than the dimerization of allyl radicals. It was not possible, however, to obtain conclusive results which would enable one to calculate the exact value of $D[(\text{CH}_2=\text{CHCH}_2)-\text{I}]$.

Comparing the kinetics of the pyrolysis of benzyl iodide with that of allyl iodide we find that the rate of decomposition of allyl iodide was higher than the rate of decomposition of benzyl iodide. From this one might draw the conclusion that $D[(\text{CH}_2=\text{CHCH}_2)-\text{I}]$ is smaller than $D(\text{C}_6\text{H}_5\text{CH}_2-\text{I})$. This conclusion is, however, by no means certain. The postulated rate-determining steps are quite different for each case,



and a closer inspection shows that the latter reaction should be faster than the former (if reaction a_2 does not involve any appreciable activation energy). In this connection we ought to emphasize that, when comparing rates of decomposition, one is entitled to draw conclusions as to the meaning of differences in bond dissociation energies only when the initial unimolecular dissociation is the rate-determining reaction.

We conclude this section with the following remarks:

(a) The pyrolysis of iodides is complicated by the occurrence of back reactions. The inertness of iodine in attacking organic molecules was considered a simplifying factor which, in practice, turned out to be the source of various difficulties.

(b) The gradation in the bond dissociation energies can be assessed if the initial dissociation process is the rate-determining step, which is not always the case.

(c) The amount of iodine produced might be decreased by the addition of I_2 to the double bond in olefins. Such a reaction might occur in the gas phase, or more likely on the glass surface.

(d) In some cases the decomposition of RI into HI and olefin might be the main process in the pyrolysis of RI. Calculation of the rate of unimolecular split into a radical and an iodine atom is then particularly doubtful. (See, for example, the results of the pyrolysis of *tert*-butyl iodide (35).)

(e) The amount of I_2 produced might be increased by the occurrence of the reaction $\text{RI} + \text{HI} \rightarrow \text{RH} + \text{I}_2$ (122). This reaction becomes particularly important when the rate of formation of HI ($\text{RI} \rightarrow \text{olefin} + \text{HI}$) is very high, for example, in the pyrolysis of *tert*-butyl iodide.

H. Determination of the C—H bond dissociation energy in toluene and related compounds

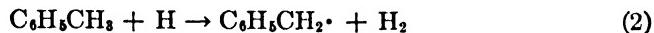
It has been shown (183, 186) that the weakest bond in the toluene molecule is the C—H bond of the methyl group. In consequence one would expect the first step in the pyrolysis of this compound to be dissociation into hydrogen atoms and benzyl radicals:



On account of their high reactivity the hydrogen atoms are rapidly removed by interaction with other molecules present in the system. If the extent of pyrolysis

is limited to a very low fraction of decomposition, then hydrogen atoms formed by reaction 1 will be surrounded mainly by the molecules of undecomposed toluene and will be, therefore, most likely to interact with these.

The experiments revealed that a hydrogen atom will react with a toluene molecule in two ways:



The first reaction produces a hydrogen molecule, while the second produces a methyl radical. The latter is surrounded by molecules of undecomposed toluene and reacts, therefore, rapidly with these, forming a methane molecule and another benzyl radical:



If the pyrolysis of toluene is carried out in a flow system, where the gases pass rapidly through the reaction vessel, then the benzyl radicals are quickly removed from the hot zone and eventually dimerize:



In order to eliminate other possible secondary reactions, it is essential to prevent the decomposition of bibenzyl, and therefore it is imperative to work with short times of contact and high rates of flow. Furthermore, it is advantageous to work with low pressure, high temperature, and low fraction of decomposition, since all these factors prevent the dimerization of benzyl radicals in the hot zone. On the other hand, numerous investigations have proved that benzyl radicals are very stable and unreactive: they neither decompose nor initiate any chain reactions (see, e.g., the pyrolysis of benzyl iodide (182), of toluene (186), of ethylbenzene (189), of benzylamine (190, 192), and of benzyl bromide (194)).

We conclude from this outline that if the pyrolysis of toluene takes place according to the above mechanism, then each mole of hydrogen or methane produced corresponds to 1 mole of toluene primarily decomposed and should be accompanied by the formation of 1 mole of bibenzyl. Moreover, the kinetics of decomposition, measured by the rate of evolution of gaseous products ($\text{H}_2 + \text{CH}_4$), should reveal all the features of a truly unimolecular reaction.

Investigation of the pyrolysis of toluene by M. Szwarc (183, 186) fully confirmed these conclusions. The pyrolysis was investigated by a flow method in the temperature range 680–850°C. and under a pressure of 2–15 mm. of mercury. The experimental technique developed for these investigations made it possible to follow the reaction down to as little as 0.01 per cent of decomposition. The only gaseous products observed were hydrogen and methane in a constant proportion (1.5:1). In addition to gaseous products bibenzyl was isolated in quantities corresponding approximately to 1 mole of bibenzyl per mole of gas formed ($\text{H}_2 + \text{CH}_4$).

The rate of reaction was calculated on the assumption that 1 mole of gas produced corresponds to 1 mole of toluene primarily decomposed. It was found that

the decomposition was a homogeneous gas reaction of the first order, the frequency factor determined experimentally being 2×10^{13} sec.⁻¹ and the activation energy 77.5 ± 1.3 kcal./mole. In view of all these facts, it seems that the author was fully justified in concluding that the estimated activation energy represents the dissociation energy of the C—H bond in toluene, i.e.:

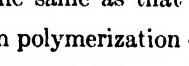
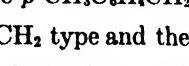
$$D(C_6H_5CH_2-H) = 77.5 \pm 1.3 \text{ kcal./mole}$$

Further confirmation for the applicability of this method of estimating C—H bond dissociation energies is based on results obtained in the pyrolysis of compounds related to toluene. The compounds listed below were pyrolyzed and the experiments seem to indicate that they decomposed according to the mechanism suggested for toluene.

	COMPOUNDS	REFERENCE
1...	<i>p</i> -, <i>m</i> -, and <i>o</i> -xylenes	M. Szwarc (186)
2...	<i>p</i> -, <i>m</i> -, and <i>o</i> -fluorotoluenes	M. Szwarc and J. S. Roberts (190)
3...	α -, β -, and γ -picolines (methylpyridines)	J. S. Roberts and M. Szwarc (151)
4...	α - and β -methylnaphthalenes and dimethylnaphthalenes	M. Szwarc and A. Shaw (200)

Let us summarize the experimental results of these pyrolyses. The gaseous products were invariably hydrogen and methane, the H₂/CH₄ ratio being similar to that observed in the decomposition of toluene. The nonvolatile products of pyrolysis were isolated and identified as the relevant homologs of bibenzyl or substituted bibenzyls. Thus: *o,o'*-dimethylbibenzyl and *m,m'*-d methylbibenzyl were isolated from the products of pyrolysis of *o*-xylene and *m*-xylene, respectively; the 2,2'-, 3,3'-, and 4,4'-difluoro-bibenzyls were isolated, identified, and described as products of pyrolysis of the respective fluorotoluenes (197); α,α' -dinaphthylethane and β,β' -dinaphthylethane were isolated and identified as products of pyrolysis of α -methylnaphthalene and β -methylnaphthalene, respectively; and the relevant dimethyldinaphthylethane was isolated and described as the product of pyrolysis of 2,6-dimethylnaphthalene (201).

The pyrolysis of *p*-xylene produced a polymer (185) and not the expected *p,p'*-dimethylbibenzyl. Nevertheless it was possible to show that the essential features of this pyrolysis remained the same as that of the toluene pyrolysis.

The polymeric substance resulted from polymerization of CH₂==CH₂, which was in turn produced by disproportionation of the primary fragments of the decomposition of *p*-xylene, i.e., the *p*-CH₃C₆H₄CH₂· radicals. The formation of molecules of the CH₂==CH₂ type and their corresponding polymers seems to be characteristic of the pyrolysis of aromatic compounds having two methyl groups in para positions. In fact, the relevant quinonoid compounds and their polymers were observed in the pyrolysis of 1,4-dimethylnaphthalene, 2-chloro- or 2-fluoro-*p*-xylene, 2,5-dimethylpyrazine, 5,8-dimethylquinoline, and 2,5-lutidine (193).

Technical difficulties prevented the identification of nonvolatile products formed in the pyrolysis of picolines. It was demonstrated, however, that the crystalline product obtained in the pyrolysis of picoline had the molecular weight of the expected dimer.

The kinetics of pyrolysis of the xylenes and of the α - and β -methylnaphthalenes was thoroughly investigated. It was shown that all these decompositions were homogeneous gas reactions of the first order, the frequency factors and activation energies being given in table 10. From these data it is obvious that frequency factors, calculated per *methyl group*, are, within the experimental error, the same for all the compounds listed.

Our confidence in this assumed mechanism and the conclusions following from it is strengthened by the above facts, which suggest that the pattern of decomposition postulated for toluene is valid not only for this single compound but for a whole class of kindred compounds. Of particular importance is the inference

TABLE 10
Pyrolysis of methylbenzenes and methylnaphthalenes

COMPOUND	ACTIVATION ENERGY kcal./mole	FREQUENCY FACTOR sec. ⁻¹
Toluene	77.3 \pm 1.3	2 \times 10 ¹³
<i>m</i> -Xylene	77.1 \pm 1.9	2 \times 2 \times 10 ¹³
<i>p</i> -Xylene	76.2 \pm 1.5	2 \times 2.5 \times 10 ¹³
<i>o</i> -Xylene	74.8 \pm 1.1	2 \times 2.5 \times 10 ¹³
α -Methylnaphthalene	73.5	1.5 \times 10 ¹³
β -Methylnaphthalene	73.5	1.5 \times 10 ¹³

drawn that the observed activation energies represent true dissociation energies of the C—H bonds in the respective compounds.

Table 11 shows computed values of the C—H bond dissociation energies. This computation was performed by assuming the frequency factor to be a constant for the series, and the actual value chosen was 2 \times 10¹³ sec.⁻¹. Justification for the use of this method of computation is discussed in Section IV,C (see page 107).

Consideration of table 11 leads to the following conclusions:

1. The substitution of an additional methyl group in the meta position in toluene seems to have no effect on the C—H bond dissociation energy. On the other hand, if this substitution takes place in the para or ortho position the C—H bond dissociation energy is weakened by 2.5 kcal./mole and 3.5 kcal./mole, respectively. This weakening effect is ascribed to hyperconjugation.
2. Substitution by a fluorine atom seems to have no effect on the C—H bond dissociation energy.
3. It seems that a change of a pyridine ring for a benzene nucleus influences the C—H bond dissociation energy, the gradation being $\gamma > \beta > \alpha$ for the three picolines.

4. A change of a naphthalene ring for a benzene ring decreases the C—H bond dissociation energy by 2.5 kcal./mole. It seems that the position of the methyl group (α or β) does not influence the C—H bond dissociation energy.

Lastly, we shall review the pyrolytic behavior of some compounds which were expected to decompose like toluene but actually behaved differently. The compounds in question are propene, 2-methylpropene ("isobutene"), cycloopen-

TABLE 11
Computed values of the C—H bond dissociation energies

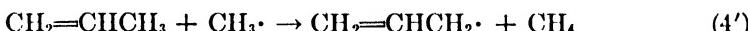
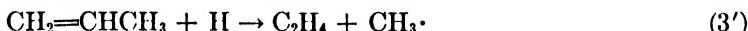
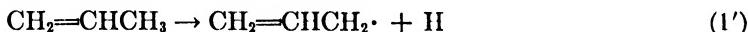
COMPOUND	FORMULA	D(C—H) IN KCAL./MOLE (TO THE NEAREST 0.5 KCAL./MOLE)
Toluene	C ₆ H ₅ CH ₂ —H	77.5 ± 0.14
<i>m</i> -Xylene.	<i>m</i> -CH ₃ C ₆ H ₄ CH ₂ —H	77.2 ± 0.18
<i>p</i> -Xylene	<i>p</i> -CH ₃ C ₆ H ₄ CH ₂ —H	74.8 ± 0.20
<i>o</i> -Xylene	<i>o</i> -CH ₃ C ₆ H ₄ CH ₂ —H	74.0 ± 0.55
<i>p</i> -Fluorotoluene	<i>p</i> -FC ₆ H ₄ CH ₂ —H	77.5–78.0
<i>m</i> -Fluorotoluene	<i>m</i> -FC ₆ H ₄ CH ₂ —H	77.5–78.0
<i>o</i> -Fluorotoluene	<i>o</i> -FC ₆ H ₄ CH ₂ —H	77.5–78.0
α -Picoline	C ₆ NH ₄ CH ₂ —H	75.5
β -Picoline	C ₆ NH ₄ CH ₂ —H	76.5
γ -Picoline	C ₆ NH ₄ CH ₂ —H	77.5
α -Methylnaphthalene	C ₁₀ H ₇ CH ₂ —H	75.0
β -Methylnaphthalene	C ₁₀ H ₇ CH ₂ —H	75.0
1,6-Dimethylnaphthalene.	CH ₂ —H H ₃ C or H—H ₂ C CH ₃	75.0
2,6-Dimethylnaphthalene	H ₃ C CH ₂ —H	75.0
2,3-Dimethylnaphthalene.	CH ₂ —H CH ₃	75.0

tadiene, and ammonia. A consideration of their pyrolysis illustrates the limitations of this method and shows up the various complicating factors which may change completely the mechanism of the decomposition.

The pyrolysis of propene was investigated by M. Szwarc (187) by the experimental technique applied previously to the pyrolysis of toluene. Hydrogen and methane were found as products of decomposition. Assuming that the rate of decomposition is measured by the rate of formation of H₂ + CH₄, it was shown

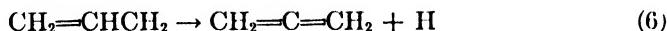
that the pyrolysis of propene was a homogeneous gas reaction of the first order, the first-order rate constant being given by $1 \times 10^{13} \exp(72,000/RT) \text{ sec.}^{-1}$. Other products of decomposition were identified as allene and ethylene. The amount of allene corresponded roughly to that of $\text{H}_2 + \text{CH}_4$ (in moles), while the quantity of ethylene seemed to be equivalent to the amount of methane.

The following mechanism, which is analogous to that suggested for the pyrolysis of toluene, accounts well for the nature of the observed products, their relative quantities, and the first order of the reaction.

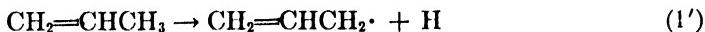


Postulation of step 1' seems reasonable, since the high resonance energy of the allyl radical should decrease considerably the C—H bond dissociation energy in propene, making the rupture of this bond more likely than the breaking of the C—C bond. Step 5' is different from the corresponding reaction 5 of the toluene scheme. The postulated disproportionation of allyl radicals accounts for the formation of allene, while step 5 would require the appearance of biallyl as the product of reaction. Reaction 1', being the rate-determining step, is responsible for the first-order kinetics and for the frequency factor of $10^{13} \text{ sec.}^{-1}$ which is characteristic for a unimolecular process. The observed activation energy of 72 kcal./mole should represent, according to the mechanism postulated, the dissociation energy of the C—H bond in propene. The latter conclusion makes this mechanism rather doubtful, as the suggested value for $D(\text{CH}_2=\text{CHCH}_2)-\text{H}$ seems to be too low, particularly since it leads to the value of 30 kcal./mole for the C—C bond dissociation energy in biallyl, a value which is obviously incompatible with the thermal stability of this compound.

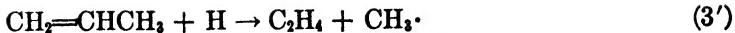
Closer comparison of the benzyl and allyl radicals reveals an important difference between them. Both radicals have high resonance energies which facilitate their formation, but the thermal stability of the benzyl radical is mainly due to the fact that it cannot be decomposed into a still more stable fragment. On the other hand, such a decomposition is possible for the allyl radical, namely:



Reaction 6 leads, of course, to the following chain mechanism:



or



Step 7 represents the termination process.²⁹

The application of the stationary-state method leads to the following expression for the rate of the overall decomposition:

$$d(\text{H}_2 + \text{CH}_4)/dt = (k_1 k_6 k_2 / k_7)^{1/2} [\text{C}_3\text{H}_8]$$

which shows that the chain mechanism also requires first-order kinetics. Moreover we may assume that $k_2 \approx k_7$, since reactions 2 and 7 probably have the same collision factor and negligible activation energies. Hence we deduce:

$$d(\text{H}_2 + \text{CH}_4)/dt = (k_1 k_6)^{1/2} [\text{C}_3\text{H}_8]$$

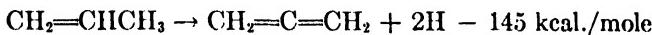
Now, since reactions 1 and 6 are unimolecular decompositions, both should require frequency factors of the order of 10^{13} sec.⁻¹; therefore the frequency factor of the overall reaction is also of the order of 10^{13} sec.⁻¹. It follows that the overall activation energy is

$$E_{\text{act}} = \frac{1}{2}(E_1 + E_6)$$

and since

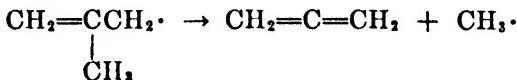
$$E_1 = D[(\text{CH}_2=\text{CHCH}_2)-\text{H}] \text{ and } E_6 = D[(\text{CH}_2=\text{CCH}_2)-\text{H}]$$

$E_1 + E_6$ is the endothermicity of the process:



This means then that the proposed chain process accounts for the nature of the decomposition products, their relative quantities, the first-order kinetics, the frequency factor, and even for the observed activation energy.

The decomposition of the allyl radical into allene and a hydrogen atom is the complicating factor which makes the mechanism of the decomposition of propene essentially different from that suggested for toluene. The similar decomposition of the methylallyl radical, i.e.,



is responsible for the fact that the pyrolysis of 2-methylpropene (188) takes a course similar to that of propene.

The estimation of the C—H bond dissociation energy in propene and 2-methyl-

²⁹ For discussion of the other termination processes see reference 187.

propene would be feasible if the length of the reaction chain could be estimated. The data provided by the decomposition of 2-methylpropene suggest that the length of the chain is approximately 10. The stationary-state method leads to the following expression for the length of the reaction chain in the decomposition of propene:

$$\ln (\text{length of chain}) = (1/2RT) \cdot (E_1 - E_6) - 1/2 \ln 3^{30}$$

Taking the length of the chain as 10, one derives

$$E_1 - E_6 \approx 11 \text{ kcal./mole}$$

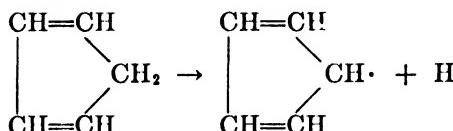
while

$$E_1 + E_6 = 145 \text{ kcal./mole}$$

(This is the endothermicity of the reaction
 $\text{CH}_2=\text{CHCH}_3 \rightarrow \text{CH}_2=\text{C}=\text{CH}_2 + 2\text{H}$)

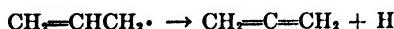
Thus $E_1 = D[(\text{CH}_2=\text{CHCH}_2)-\text{H}] \approx 78 \text{ kcal./mole}$. This result seems to be plausible and leads to the frequency factor $2.5 \times 10^{13} \text{ sec.}^{-1}$ for the initial decomposition process, a value which is in agreement with the results discussed previously (see page 131). Similar considerations lead to $D[(\text{CH}_2=\text{CCH}_2)-\text{H}] = 76 \text{ kcal./mole}$ and $5 \times 10^{13} \text{ sec.}^{-1}$ for the frequency factor of the initial decomposition of 2-methylpropene. It must be emphasized, however, that these results are highly speculative and they call for an additional and independent evidence. Such evidence has been provided recently by a study of the pyrolysis of 1-butene (199; see also page 141).

A few experiments with cyclopentadiene were carried out in the Manchester laboratories, the technique described above being used again (unpublished results). It was expected that the molecule of cyclopentadiene would split into a hydrogen atom and the C_5H_5 radical

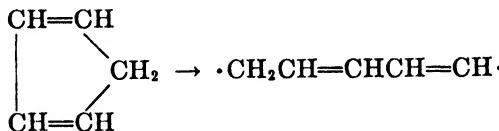


and that the hydrogen atoms would react with the excess of cyclopentadiene, producing H_2 and C_5H_5 radicals. It was also anticipated that the C_5H_5 radicals would be stable enough to emerge from the reaction vessel unchanged and eventually to dimerize. It was found, however, that a complete cracking of the molecule took place. The products of the decomposition contained H_2 , CH_4 , C_2 hydrocarbons, etc. No attempt was made to clear up the mechanism of this

³⁰ $\ln 3$ appears in this expression because statistical considerations require that the frequency factor of the decomposition of the C—H bond in the methyl group of propene be three times as great as for the decomposition:



pyrolysis. It may well be that the molecule breaks up by the scission of a C—C bond, i.e.,



with the subsequent decomposition of the diradical thus formed.

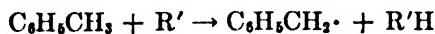
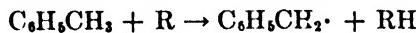
The thermal decomposition of ammonia (190) proved to be another instance of a pyrolysis from which no information on bond dissociation energy was obtained. It was expected that it would be possible to break the N—H bond and to produce hydrogen atoms and NH₂ radicals. Further, it was supposed that hydrogen atoms would react with ammonia, producing H₂ and more NH₂ radicals, and that the latter would dimerize in the outlet tube. The reaction, however, proved to be heterogeneous, a result which confirms the earlier observations of C. N. Hinshelwood and E. R. Burk (82), the products being H₂ and N₂ in the molar ratio of 3:1. Moreover, it is known that NH₂ radicals decompose rather than dimerize, and the products of their decomposition are H₂ and N₂.

I. The determination of bond dissociation energy by the "toluene carrier gas" technique

In the preceding section we described a method of estimating the C—H bond dissociation energy which can be summarized as follows: (1) Hydrogen atoms produced in the decomposition are rapidly removed from the system, forming H₂ (or CH₄) and thermally stable benzyl radicals (or their homologs or derivatives). (2) The benzyl radicals being inert and thermally stable neither decompose nor react, but pass out from the system when they eventually dimerize outside the hot zone. Therefore, no chain reaction ensues and the rate of formation of H₂ (and CH₄) measures the rate of initial decomposition of the compound investigated.

This method, with slight modifications, applies to the investigation of the pyrolysis of a number of compounds which split into two radicals by the breaking of one bond only. The technique is limited, however, by the condition that the dissociation energy of the bond in question must be smaller (preferably much smaller) than the C—H bond dissociation energy in toluene.

Let us assume that a molecule R—R' decomposes by the rupture of the R—R' bond into radicals R and R', and that D(R—R') is smaller than D(C₆H₅CH₂—H) i.e., smaller than 77 kcal./mole. We can, therefore, carry out the dissociation process RR' → R + R' at temperatures low enough to avoid the decomposition of toluene, which is used in this technique as a carrier gas. The radicals R and R', being surrounded by molecules of toluene, are removed rapidly from the system by the reactions:

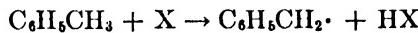


In the experimental set-up (similar to that described in the preceding section) the benzyl radicals pass out of the reaction vessel and eventually dimerize outside the hot zone. We conclude, therefore, that if the pyrolysis of RR' takes place according to the scheme suggested above, then the rate of initial decomposition may be measured by the rate of formation of RH, or R'H, or bibenzyl. Moreover, the molecular ratio of RH:R'H:bibenzyl ought to be 1:1:1.

The appearance of bibenzyl amongst the products of decomposition makes it possible to discriminate between two modes of decomposition: namely, the decomposition into radicals (or atoms) and the decomposition into molecules. For example, ethyl bromide might decompose into ethyl radicals and bromine atoms, or into ethylene and hydrogen bromide. By using toluene as a carrier gas we should obtain bibenzyl as one of the products of reaction only if the decomposition takes place *via* radicals, whereas no bibenzyl would be produced if the compound decomposes directly into two molecules.

The most suitable compounds for this type of investigation are the benzyl derivatives of the general formula C₆H₅CH₂X, where X denotes an atom or a radical. The high resonance energy of the benzyl radical decreases considerably the C—X bond dissociation energy, making possible pyrolysis at conveniently low temperatures. Furthermore, the overall process is simplified by the fact that there is one radical (or atom) only, namely, X, which has to be removed from the system. The second fragment—the benzyl radical—remains unchanged and eventually gives rise to bibenzyl.

The important condition for the successful operation of the method is the high reactivity of X, which has to be removed rapidly from the system by the reaction:

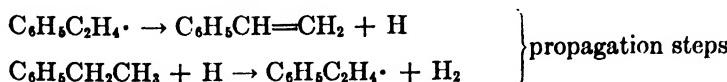
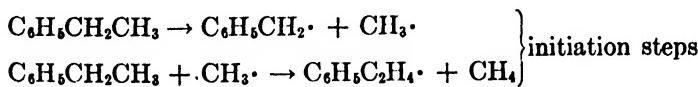


For example, the method fails in the case of benzyl iodide because the iodine atoms produced by the initial decomposition are too inert and unable, therefore, to react with toluene and to produce hydrogen iodide. This failure leads in consequence to back reaction and eventually to the equilibrium:



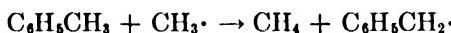
which has been discussed on page 127.

The method was successfully applied in the pyrolysis of ethylbenzene (189), benzyl bromide (194), and benzylamine (192). The pyrolysis of ethylbenzene illustrates how the kinetics of decomposition could be simplified by using toluene as a carrier gas. The decomposition of ethylbenzene without carrier gas led to a chain reaction:



and some termination steps. Styrene and hydrogen are the main products of the pyrolysis required by the above mechanism. It was found, in fact, that the bulk of nongaseous material was composed of styrene, with small quantities of bibenzyl; the main gaseous product was hydrogen, which was present along with small quantities of methane and C₂ hydrocarbons (the latter resulted probably from some chain termination process; for example, CH₃· + CH₃· → C₂H₆, or C₆H₅C₂H₅ + H → C₆H₆ + C₂H₆·). The kinetics of the decomposition was hopelessly complicated and difficult to disentangle.

The character of the pyrolysis was changed radically when toluene was used as a carrier gas. The formation of the C₆H₅C₂H₄· radical, which was responsible for the chain propagation, was prevented by the reaction between methyl radicals and toluene:



Since toluene was in great excess, the chance of reaction between methyl radicals and toluene was much higher than between methyl radicals and ethylbenzene. In consequence the products of the pyrolysis were methane and bibenzyl in molar proportions (1:1). The kinetics of the decomposition, measured by the rate of formation of methane, obeyed the first-order law, the activation energy being 63 kcal./mole and the frequency factor 1×10^{13} sec.⁻¹ It was concluded, therefore, that the rate of formation of methane measures the rate of initial decomposition of ethylbenzene into methyl and benzyl radicals and the observed activation energy of 63 kcal./mole represents the C—C bond dissociation energy in ethylbenzene.

There is a check on the values obtained for $D(\text{C}_6\text{H}_5\text{CH}_2-\text{H})$ and $D(\text{C}_6\text{H}_5\text{CH}_2-\text{CH}_3)$. These two values, in conjunction with the relevant thermochemical data, make it possible to estimate the dissociation energy of the first C—H bond in methane at 103 ± 3 kcal./mole, and the results are in accordance with the $D(\text{CH}_3-\text{H})$ estimated by other investigators, and particularly with the determination of G. B. Kistiakowsky and E. R. Van Artsdalen (88) (101 ± 1 kcal./mole).

The pyrolysis of benzyl bromide (194), investigated by the same technique, produced hydrogen bromide and bibenzyl in molar proportions of 1:1. The kinetics of the decomposition revealed all the characteristic features of a unimolecular reaction, obeying the first-order law and giving a frequency factor of the order of 10^{13} sec.⁻¹ The observed activation energy of 50.5 kcal./mole was identified, therefore, with the C—Br bond dissociation energy in benzyl bromide. It was again possible to check the deduction by using the available thermochemical data. The difference between $D(\text{C}_6\text{H}_5\text{CH}_2-\text{H})$ and $D(\text{C}_6\text{H}_5\text{CH}_2-\text{Br})$ was estimated calorimetrically by O. H. Gellner and H. A. Skinner (61) at 29 ± 3 kcal./mole. Since the direct pyrolytic estimation of both bond dissociation energies gave 77.5 ± 1.3 kcal./mole for the former and 50.5 ± 2 kcal./mole for the latter, the difference expected is 27 ± 3.3 kcal./mole. The agreement seems to be satisfactory.

The pyrolysis of benzylamine (192), investigated again by the same technique,

produced ammonia and bibenzyl. This decomposition also revealed the characteristic features of the unimolecular reaction, and therefore the observed activation energy of 59 ± 4 kcal./mole was identified with the C—N bond dissociation energy in benzylamine.

The above technique was applied to investigations of the pyrolysis of other classes of compounds such as hydrazine (191), biacetyl (195), 1-butene (199), and a series of organic bromides (unpublished results).

The pyrolysis of hydrazine (191) provided an example of a mixed heterogeneous-homogeneous decomposition. It is well known that hydrazine decomposes heterogeneously into nitrogen and ammonia, or into nitrogen, hydrogen, and ammonia, according to the following stoichiometric equations:



The first mode of decomposition is predominant in reactions which take place on the surfaces of glass or silica, while the second represents the main reaction which takes place on the surfaces of platinum or tungsten wire. It was also demonstrated that the heterogeneous decomposition obeyed first-order kinetics.

The investigation of the pyrolysis of hydrazine at much higher temperatures, i.e., 660–780°C., revealed that in addition to the heterogeneous decompositions mentioned a homogeneous reaction took place in which a molecule of hydrazine dissociated into two NH₂ radicals.



It was possible to investigate this homogeneous reaction by using toluene as a carrier gas, since under these conditions the NH₂ radicals reacted with toluene, producing eventually bibenzyl. Hence the rate of formation of bibenzyl measured the rate of homogeneous dissociation (h₃).

The products of the pyrolysis contained, therefore, nitrogen, hydrogen, ammonia, and bibenzyl. Assuming that all the observed hydrogen was produced by reaction h₂, it was possible to calculate the amount of hydrazine decomposed and ammonia formed in this reaction. Nitrogen was formed in both reactions h₁ and h₂; deducting therefore from the total amount of nitrogen observed the amount of hydrogen (calculated in moles), one obtains the amount of nitrogen produced in reaction h₁. Thus it was possible to compute the amount of hydrazine decomposed and of ammonia formed in this reaction. Finally the amount of hydrazine decomposed and of ammonia formed in the homogeneous reaction (h₃) could be calculated from the amount of bibenzyl observed. Thus it was possible to calculate the total amount of ammonia formed in the pyrolysis and the total amount of hydrazine decomposed. Since both these quantities were observable, the above deductions could be checked. Table 12 illustrates the above method of computation. The activation energy of the homogeneous dissociation process (h₃) was estimated at 60 kcal./mole and the frequency factors at $4 \times 10^{12} \text{ sec.}^{-1}$. Making the usual assumption, that the activation energy of the

recombination process is negligible, it was deduced that $D(\text{NH}_2-\text{NH}_2) = 60 \text{ kcal./mole}$.

The results obtained in the investigation of the pyrolysis of hydrazine may be checked against the results obtained in the pyrolysis of benzylamine, since having $D(\text{NH}_2-\text{NH}_2)$ and $\Delta H_f(\text{N}_2\text{H}_4)$ one is able to calculate $\Delta H_f(\text{NH}_2\cdot)$, and the latter value can be independently calculated from $D(\text{C}_6\text{H}_5\text{CH}_2-\text{NH}_2)$, $\Delta H_f(\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2)$, and $\Delta H_f(\text{C}_6\text{H}_5\text{CH}_2\cdot)$. The calculation based on the estimated value of $D(\text{NH}_2-\text{NH}_2)$ leads to $\Delta H_f(\text{NH}_2\cdot) = 41 \pm 2 \text{ kcal./mole}$, while that based on $D(\text{C}_6\text{H}_5\text{CH}_2-\text{NH}_2)$ gives $\Delta H_f(\text{NH}_2\cdot) = 35 \pm 5 \text{ kcal./mole}$. The latter value relies on $\Delta H_f(\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2)$ estimated by combustion by Petit (133a) in 1889. If the heat of combustion which he obtained was too low—which seems likely⁴¹—then the corrected value of $\Delta H_f(\text{NH}_2\cdot)$ would be higher, making the agreement between both methods of computation still closer.

TABLE 12

OBSERVED AMOUNT millimoles	EQUATION OF DECOMPOSITION	NH ₃ CALCULATED millimoles	N ₂ H ₄ DECOMPOSED millimoles
H ₂ . . . 0.25	2N ₂ H ₄ = H ₂ + N ₂ + 2NH ₃	2 × 0.25 = 0.50	2 × 0.25 = 0.50
N ₂ . . . 0.43 = 0.25 + 0.18	3N ₂ H ₄ = N ₂ + 4NH ₃	4 × 0.18 = 0.72	3 × 0.18 = 0.54
Bibenzyl 0.48	N ₂ H ₄ = 2NH ₂ (1 bibenzyl)	2 × 0.48 = 0.96	1 × 0.48 = 0.48
Total		NH ₃ = 2.18	N ₂ H ₄ = 1.52
Observed		NH ₃ = 2.02	

The pyrolysis of biacetyl (195) yields carbon monoxide and methane in the molar proportion 1:1. The amount of biacetyl decomposed was estimated as a difference between the amounts of biacetyl introduced and recovered (i.e., not decomposed), the latter two entities being determined directly. It was found in this way that each mole of biacetyl decomposed produced 2 moles of carbon monoxide and 2 moles of methane. These facts suggested that the mechanism of the decomposition of biacetyl is represented by the following equations:



and that the rate of formation of CO + CH₄ measures the rate of initial decomposition of biacetyl, which was found to obey the first-order kinetics. Hence, the activation energy estimated at 60 kcal./mole represents the CH₃CO—COCH₃ bond dissociation energy.

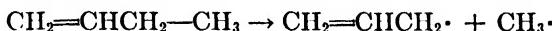
The value of $D(\text{CH}_3\text{CO}-\text{COCH}_3)$, in conjunction with the heat of formation of biacetyl, yields the heat of formation of the acetyl radical, which was computed

⁴¹ The minute amount of water or carbon dioxide which is likely to be in benzylamine makes the heat of combustion too low (0.5 per cent of either of these decreases the heat of combustion by about 5 kcal./mole).

at -11 kcal./mole. Having this value it was possible to calculate the various $\text{CH}_3\text{CO}-\text{X}$ bond dissociation energies from the relevant thermochemical data only.

The above value for the heat of formation of the acetyl radical was confirmed by the estimation of $D(\text{C}_6\text{H}_5\text{CH}_2-\text{COCH}_3)$. The pyrolysis of the latter compound was investigated also by the "toluene carrier gas" technique (195), and it was found to proceed analogously to the pyrolysis of biacetyl. The value of $D(\text{C}_6\text{H}_5\text{CH}_2-\text{COCH}_3)$ was estimated at ~ 63 kcal./mole, and this, together with the required thermochemical data, led to $\Delta H_f(\text{CH}_3\text{CO}\cdot) \approx 10$ kcal./mole, in fair agreement with the previous estimate deduced from studies of the pyrolysis of biacetyl.

The pyrolysis of 1-butene (199) was similar to the pyrolysis of ethylbenzene. The initial decomposition produced methyl and allyl radicals:



Methyl radicals were removed by toluene and the progress of decomposition was measured, therefore, by the rate of formation of methane. The $\text{CH}_2=\text{CHCH}_2-\text{CH}_3$ bond dissociation energy was estimated at 62 kcal./mole, and this value led to $D[(\text{CH}_2=\text{CHCH}_2)-\text{H}] = 77$ kcal./mole. The latter C—H bond dissociation energy was estimated previously by investigating the kinetics of the decomposition of propene. These studies suggested a value of 78 kcal./mole for $D[(\text{CH}_2=\text{CHCH}_2)-\text{H}]$, which compares well with that obtained from investigations of the pyrolysis of 1-butene.

J. Dissociation energies of RO—NO bonds

E. W. R. Steacie and his collaborators investigated the kinetics of the pyrolysis of a series of organic nitrites, *viz.*, methyl (171), ethyl (172), *n*-propyl (173), isopropyl (174), and *n*-butyl nitrites (175). All these decompositions were studied by a static method over the temperature range of 170–230°C., the rate of reaction being measured by an increase of pressure. By packing the reaction vessel with short silica tubes (which increased the surface/volume ratio by a factor of 6–9) it was proved that all these processes were homogeneous gas reactions. Assuming that the increase of pressure was proportional to the amount of compound decomposed, Steacie deduced that all these pyrolyses followed the first-order law. This deduction was substantiated by the following two criteria:

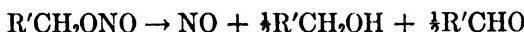
1. The time required for an increase in pressure by some constant fraction of its initial value was constant. This meant that the time for partial decomposition was independent of the initial pressure.

In most cases the constancy of the time for fractional decomposition was found to hold for initial pressures ranging from 50 to 350 mm. of mercury, and in the case of methyl nitrite even for higher pressures, up to 35 atm. (170).

2. The plot of the increase in pressure against time was in close agreement with the theoretically expected graph for a first-order reaction. This was further checked by comparing ratios of $t_{50\%}/t_{25\%}$, as obtained from ex-

periments, with the theoretical values for the same ratios derived on the basis of first-order kinetics. For example, in the decomposition of methyl nitrite the ratio of the times required to increase the pressure by 50 per cent and 25 per cent of the initial pressure was found to be 2.53. The final increase of pressure was 82.5 per cent of the initial pressure. Thus, the above increments of pressure correspond to 30.3 per cent and 60.6 per cent of the total decomposition. The theoretical value of $t_{60.6\%}/t_{30.3\%}$ is 2.58, in excellent agreement with the experimental value of 2.53.

The investigations also included the analysis of the products of each reaction. Although the analytical technique was rather crude, Steacie was able to conclude that the overall process of decomposition was represented stoichiometrically by the equation:



Finally, the activation energies of these processes were estimated in the usual way from the temperature coefficients of the time of fractional decomposition. The results are summarized in table 13.

TABLE 13
Activation energies of decomposition of organic nitriles

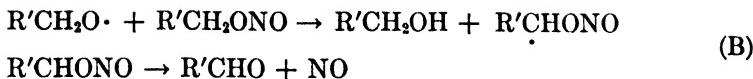
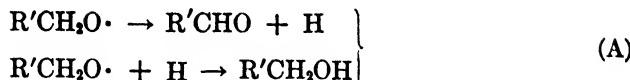
COMPOUND	ν	E
	sec. ⁻¹	kcal./mole
CH_3ONO	1.8×10^{13}	36.4
$\text{C}_2\text{H}_5\text{ONO}$	1.4×10^{14}	37.7
$n\text{-C}_3\text{H}_7\text{ONO}$	2.7×10^{14}	37.6
$\text{Iso-C}_3\text{H}_7\text{ONO}$	1.3×10^{14}	37.0
$n\text{-C}_4\text{H}_9\text{ONO}$	10^{13}	36.0

It follows from what was said that the decompositions of organic nitriles are homogeneous gas reactions of the first order, the frequency factor of the rate constants being 10^{13} – 10^{14} sec.⁻¹. Consequently, Steacie concluded that all these pyrolyses are initiated by the same unimolecular split of the molecule of the organic nitrite. The results of the analysis of the products proves that the following reaction is the only possible³² primary step, as suggested by Steacie:



This primary reaction must be followed by a sequence of rapid processes which remove the $\text{R}'\text{CH}_2\text{O}\cdot$ radicals. Several reaction schemes may be proposed which take these points into account.

* One would expect the dissociation of the molecule of RONO to occur by the rupture of the RO–NO bond, because this bond seems to be the weakest one in the molecule of the organic nitrite.



Scheme A, originally proposed by Steacie and workers (171), does not seem to be likely. If a hydrogen atom is formed, then one expects it to have a much higher chance of collision with a molecule of the undecomposed nitrite than with an $\text{R}'\text{CH}_2\text{O}\cdot$ radical, since the concentration of these radicals is very much smaller than that of the undecomposed nitrite. Therefore, the probability of reaction D



would be very considerable, and this reaction could be neglected only if it either has a very high activation energy, or if the stationary concentration of $\text{R}'\text{CH}_2\text{O}\cdot$ radicals is very high. However, neither alternative seems to be acceptable.

Scheme C leads to the same result as scheme A, and yet it does not involve the improbable implications of the latter, but it requires a great stability of the $\text{R}'\text{CH}_2\text{O}\cdot$ radicals.

Scheme B, proposed by F. O. Rice and E. L. Rodowskas (148), seems to be the most plausible. It implies that the observed reaction rate is twice as high as the initiation rate, leaving all the other features of the kinetics identical with those required by the previous schemes. It is obvious, however, that all three schemes account equally well for the observed products of the reaction and for its unimolecular character.

The unimolecular character gains additional support from the studies of F. O. Rice and E. L. Rodowskas (148). These workers investigated the pyrolysis of ethyl nitrite in the region 400–500°C., using the mirror technique and carbon dioxide as a carrier gas. The activation energy was estimated by them as 35 ± 3 kcal./mole, and it was attributed to the initial rupture of the molecule of $\text{C}_2\text{H}_5\text{ONO}$ into a $\text{C}_2\text{H}_5\text{O}\cdot$ radical and an NO molecule. The radicals removing the mirror were identified as $\text{CH}_3\cdot$, which can be interpreted in terms of the decomposition of the $\text{CH}_3\text{CH}_2\text{O}\cdot$ radical into a $\text{CH}_3\cdot$ radical and a CH_2O molecule. The high temperature of the pyrolysis and the dilution of ethyl nitrite with carbon dioxide favor the degradation of the $\text{CH}_3\text{CH}_2\text{O}\cdot$ radical, as suggested above.³³

In the light of all these facts one may safely conclude that the activation energy of the dissociation process



³³ The experiments of Rice and Rodowskas also demonstrate that in the absence of the carbon dioxide carrier no methyl radicals are produced.

is of the order of 34–37 kcal./mole. It is well established that the recombination of various radicals with nitric oxide molecules proceeds extremely easily, and this implies that the activation energy of the recombination process is very small, perhaps even zero. Hence, one arrives at the final result: *The dissociation energy of the RO—NO bond is of the order of 34–37 kcal./mole.*

There remains a further point to be elucidated: namely, the influence of the variation of the radical R in the nitrite molecule on the dissociation energy of the RO—NO bond. The activation energies listed in table 13 are not accurate enough to provide a satisfactory answer, and it is suggested that the problem might be solved by comparing the rate constants of decompositions of various nitrites, measured at the same temperature. On the assumption of a *constant frequency factor* the ratio of the rate constants leads to the difference in the dissociation energies of the various RO—NO bonds. The necessary data are provided in the paper by E. W. R. Steacie and W. McF. Smith (175) (table 14).

TABLE 14
Dissociation energies of RO—NO bonds

COMPOUND	RATE CONSTANT AT 190°C.		ΔD kcal./mole
	sec. ⁻¹		
CH ₃ O—NO	0.97×10^{-4}		(0)
C ₂ H ₅ O—NO	1.9×10^{-4}		-0.6
n-C ₃ H ₇ O—NO	3.9×10^{-4}		-1.3
Iso-C ₃ H ₇ O—NO	3.7×10^{-4}		-1.2
n-C ₄ H ₉ O—NO	8.9×10^{-4}		-1.9

Inspection of table 14 shows that the rate constant increases, i.e., the bond dissociation energy decreases, in the series methyl, ethyl, propyl, butyl. Closer examination of Steacie's results, however, casts some doubts on the accuracy of the values quoted in table 14. The decompositions of nitrites are certainly accompanied by various side reactions, which may considerably affect the numerical results obtained from measurements of the increase of pressure. Some of the disconcerting factors are summarized as follows:

1. The suggested mechanism requires the final pressure to be twice the initial pressure. Actually the increase of pressure amounts only to 82 per cent for methyl nitrite, 86 per cent for ethyl nitrite, and it varies from 60 to 80 per cent in the case of butyl nitrite. (For n-propyl nitrite and isopropyl nitrite the increase of pressure reached the theoretically required value of 100 per cent.)
2. In some experiments a drop of pressure was observed in the last period of reaction, and in these cases it was necessary to consider the maximum value of the pressure as the final pressure.
3. The postulated mechanism requires all the noncondensable gas to be nitric oxide. In fact, the noncondensable gas obtained in the decomposition of methyl nitrite contained 81–88 per cent of nitric oxide and 6–10 per cent of carbon monoxide; that obtained from ethyl nitrite contained

88–94 per cent of nitric oxide and 1–3 per cent of carbon monoxide; that from *n*-propyl nitrite contained 90 per cent of nitric oxide; and that from isopropyl nitrite contained 82–84 per cent of nitric oxide.

4. The case of *n*-propyl nitrite is particularly doubtful, as considerable amounts of tarry materials and of carbon were deposited in the reaction bulb, the results being much less reproducible than those obtained for the lower nitrites.
5. The unimolecular rate constants calculated for the various periods of reaction were sometimes different; e.g., in the decomposition of ethyl nitrite the rate constant increased slightly towards the end of reaction, while in the decomposition of isopropyl nitrite it dropped considerably as the reaction proceeded.
6. A later investigation by A. G. Carter and M. W. Travers (38) demonstrated that the rate of production of nitric oxide resulting from the decomposition of methyl nitrite could not be represented by any simple kinetic expression. In the words of these workers there is ". . . no justification for the statement that it [the decomposition] involves a first order reaction."

This last statement of Travers is, in our opinion, debatable, and we consider it most likely that the decomposition of organic nitrites in the main is governed by the unimolecular reaction:



However, the disturbing factors listed above make the data presented by Steacie and his collaborators too uncertain for any conclusions to be drawn from them about the influence of the nature of R on the dissociation energy of the RO—NO bond. The present writer is inclined to believe that $D(\text{RO}-\text{NO})$ is of the order of 34–37 kcal./mole, probably tending towards the lower limit. It seems also that the dissociation energy of the RO—NO bond decreases along the series methyl, ethyl, propyl, butyl, but this trend is by no means established. The problem might be solved if it were possible to compare the *initial rates* of decomposition of various nitrites measured at the same temperature, which should be as low as possible.

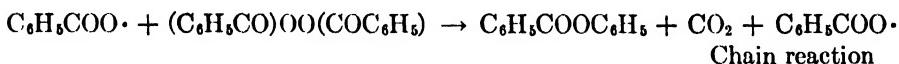
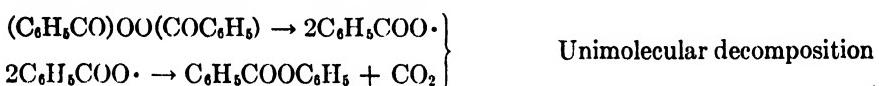
K. The O—O bond dissociation energy in peroxides

The dissociation energy of the O—O bond in hydrogen peroxide has been estimated at 55 kcal./mole from the thermochemical data in conjunction with the measured value of $D(\text{H}-\text{OH})$. It seems, however, that the O—O bond dissociation energies in organic peroxides are considerably lower than $D(\text{H}_2\text{O}_2)$, although the existing observations do not permit one to draw any definite conclusions.

The kinetics of the thermal decomposition of various organic peroxides convinces us that the first step in these processes is the rupture of the O—O bond. Unfortunately, this primary dissociation is followed by various secondary reactions which complicate the overall kinetics to such an extent that the estima-

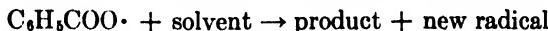
tion of the activation energy of the initial dissociation from the overall activation energy is subject to considerable uncertainties. We may illustrate this point by discussing the kinetics of the thermal decomposition of benzoyl peroxide, acetyl peroxide, ethyl peroxide, propyl peroxide, and tertiary butyl peroxide.

The decomposition of benzoyl peroxide has been investigated by many workers. It has been shown that this decomposition produces carbon dioxide, benzoic acid, phenyl benzoate, and various other products, not all of which were identified. The first kinetic studies were performed by D. J. Brown (29), by F. I. Berezovskaya and E. K. Varfolomeeva (17), and by S. Kamenskaya and S. Medvedev (86) in 1940. The rate of reaction was measured by the rate of disappearance of peroxides. The reaction was found to be approximately of the first order, and the activation energy measured by the temperature coefficient of the overall process (over the temperature range 75–85°C.) was estimated at 30 kcal./mole (86). The very extensive studies of K. Nozaki and P. D. Bartlett (121) demonstrated that the overall process can be represented by two simultaneous reactions—a unimolecular decomposition and a chain reaction which obeys a kinetic of the 3/2 or second order. They suggested the following mechanism in order to account for the observed facts:



The existence of a chain reaction was proved by demonstrating inhibition and initiation phenomena. The component rate constants for the unimolecular and chain reactions were computed from the overall kinetics, and the activation energies of the unimolecular dissociation were estimated at 30.7 kcal./mole and at 33.3 kcal./mole for decompositions taking place in acetic anhydride and benzene, respectively. The corresponding frequency factors of the unimolecular steps in the two solvents were calculated to be 6×10^{14} sec.⁻¹ and about 10^{16} sec.⁻¹. It is to be noted that the rate of the reaction depended on the nature of the solvent used (compare references 10 and 121), and it is most unfortunate that, owing to the low volatility of benzoyl peroxide, the reaction has not been investigated in the gaseous phase.

The complicating action of the solvent is caused by the chain-transfer reaction:



followed by the secondary chain process initiated by new radicals. One might expect, however, that if the above reaction leads to a stable radical, then the latter would terminate the chain process, and thus the rate of inhibited reaction would measure the rate of the initial dissociation. It was our belief that such a

simplification of the process would be brought about by using toluene as a solvent, but the results of P. D. Bartlett and R. Altschul (9) and of K. Nozaki and P. D. Bartlett (121) did not confirm this expectation.

The importance of the chain process would be reduced in more dilute solutions, but the work of P. F. Hartman, H. G. Sellers, and D. Turnbull (74), who investigated the decomposition of benzoyl peroxide at various concentrations (the lowest concentration being 0.005 mole/liter) did not reveal any simplification of the reaction scheme. The results of these workers agreed very well with those obtained by Nozaki and Bartlett, and the activation energies and frequency factors reported by Turnbull *et al.* are presented in table 15.

TABLE 15
Frequency factor for the decomposition of benzoyl peroxide

SOLVENT	CONCENTRATION	E	ν
		moles/liter	sec. ⁻¹
Benzene	0.0050		
Benzene	0.025	29.9	1×10^{14}
<i>tert</i> -Butylbenzene	0.012	30.4	2×10^{14}
Cyclohexane	0.012	28.2	3×10^{13}
Methylcyclohexane	0.012	30.7	6×10^{14}
<i>n</i> -Octane	0.008	29.0	3×10^{13}

TABLE 16
Unimolecular rate constants for the decomposition of benzoyl peroxide

TEMPERATURE	<i>k</i> × 10 ⁴	TEMPERATURE	<i>k</i> × 10 ⁴
°C.	sec. ⁻¹	°C.	sec. ⁻¹
54*	1.83	80	33.5
64*	5.84	90	110.0
74*	19.3		

* These results were obtained by S. G. Cohen (40).

D. J. Brown (30) presented in his paper the data for the unimolecular rate constants (see table 16), covering a great range of temperature, and we may use them for the more accurate computation of activation energy and frequency factor. This leads to an activation energy of about 27.5 kcal./mole and a frequency factor of about 3×10^{12} sec.⁻¹.

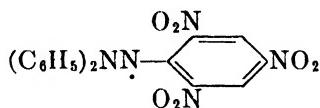
Investigations by B. Barnett and W. E. Vaughan (8) proved again that the decomposition of benzoyl peroxide is a composite reaction and can be treated as strictly of the first order only in infinitely dilute solutions. The activation energy of the first-order reaction in infinitely dilute solution was estimated at 31–32 kcal./mole. The rate of the reaction depended on the nature of the solvent, varying by a factor of 20.

All the data mentioned above indicate that the primary dissociation process



corresponds to an activation energy of about 27–33 kcal./mole. Since we favor a low value for the frequency factor (10^{12} – 10^{13} sec. $^{-1}$), we therefore recommend the value 27–28 kcal./mole as a more reliable estimate for the above activation energy. Making the usual assumption that the recombination process does not require any activation energy we estimate $D(C_6H_5COO—OCOC_6H_5)$ at about 27–28 kcal./mole. This estimate, however, would be too low if the observed rate of reaction were given by the product of the rate of initiation and the length of the chain, e.g., a chain of about 100 cycles would make the “true” dissociation energy higher by about 3 kcal./mole.

An extremely elegant method of measuring the rate of dissociation of peroxides was developed by C. E. H. Bawn and Mellish³⁴ (13). These workers found that the stable and colored radical



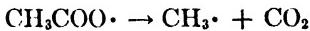
is removed easily from solution by other radicals formed in the system, e.g., by radicals produced in the decomposition of benzoyl peroxide. Hence, the rate of the initial decomposition of peroxide is measured by the rate of disappearance of $(C_6H_5)_2NNC_6H_2(NO_2)_3$, and the latter might be followed by any colorimetric method. Using this method Bawn and Mellish estimated $D(C_6H_5COO—OCOC_6H_5)$ at about 35 kcal./mole. The frequency factors were of the order 10^{14} – 10^{16} sec. $^{-1}$, and the rate of dissociation was found to depend on the nature of the solvent.

The kinetics of the thermal decomposition of substituted benzoyl peroxides was investigated by D. J. Brown (30). The rate of decomposition of substituted peroxides was of the same order as the rate of decomposition of the unsubstituted compound. This seems to indicate that the influence of substitution on the O—O bond dissociation energy in benzoyl peroxides is not very considerable.

The thermal decomposition of acetyl peroxide was investigated both in the gaseous phase and in solution by O. J. Walker and G. L. E. Wild (209). The decomposition in the gaseous phase, at 100°C., produced ethane and carbon dioxide in the molar proportion 1:2, and Walker and Wild explained this result by postulating a reaction



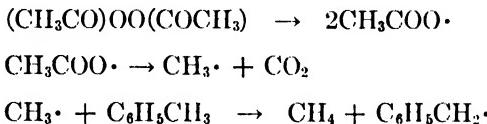
The same products, however, would be obtained in a chain reaction:



³⁴ I am indebted to Professor Bawn for permission to quote his unpublished results.

It is most unfortunate that the above workers did not report the rate of the gaseous decomposition.

The liquid-phase decomposition of acetyl peroxide was investigated in toluene solution. The products of decomposition were different from those obtained in the gaseous phase, consisting mainly of methane and carbon dioxide in a molar ratio of about 1:1. Kinetically the reaction was of the first order, the activation energy being estimated at 31 kcal./mole (the frequency factor was 8×10^{14} sec.⁻¹). It seems, therefore, that the decomposition could be represented by the following mechanism:



the initial dissociation being the rate-determining step. If this mechanism is correct, then the O—O bond dissociation energy in acetyl peroxide would be about 31 kcal./mole.

The kinetics of the thermal decompositions of diethyl peroxide and dipropyl peroxide has been investigated by E. J. Harris and A. C. Egerton (72) and by E. J. Harris (71). Both reactions were proved to be homogeneous, first-order, gaseous decompositions, the rate being measured manometrically. The first-order rate constants remained unchanged over a wide range of initial pressure and were not influenced by the presence of foreign gases. As the initial pressure was raised, the character of the reaction suddenly changed at a definite value and became explosive. The nonexplosive decompositions of both substances had definite although very short induction periods. The experimental activation energy for the decomposition of diethyl peroxide was estimated at 31.5 kcal./mole, the frequency factor being 5×10^{14} sec.⁻¹; the corresponding values for dipropyl peroxide were 36.5 kcal./mole and 25×10^{14} sec.⁻¹. It seems very likely that the rate-determining step in these decompositions is the rupture of the O—O bond and that the above activation energies are equal to the corresponding O—O bond dissociation energies. The last conclusion, however, is not definite, because the mechanism of the decomposition is not yet quite clear. Harris suggested:



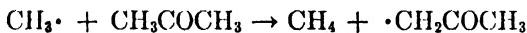
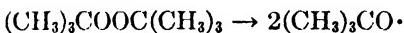
This suggestion is contradicted by the fact that in the decomposition of diethyl peroxide the final pressure increases to 2.17 times the initial pressure and in the decomposition of dipropyl peroxide to 2.5 times the initial pressure. More work is required for the determination of the O—O bond dissociation energy in these compounds.

The decomposition of tertiary butyl peroxide, investigated by N. A. Milas and D. M. Surgenor (1946) in a flow technique at temperature of 200–300°C., produced acetone and ethane. This finding can be understood in the light of the suggestion of P. George and A. D. Walsh (62) that the decomposition of a

tertiary peroxide takes place by the breaking of the O—O bond, followed by the reaction:



The kinetics of the thermal decomposition of tertiary butyl peroxide was very thoroughly investigated by W. E. Vaughan and his colleagues. The work conducted in the liquid phase (142) demonstrated the presence of $(CH_3)_3CO \cdot$ radicals, since $(CH_3)_3COH$ was isolated amongst the products of decomposition. The studies in the gaseous phase (141) were carried out by a static manometric technique and by a flow technique, the latter being used only for the estimation of products. Thus it was shown that acetone and ethane were the main products of decomposition, accompanied by much smaller amounts of methane and methyl ethyl ketone, and the appearance of these products was accounted for by the following mechanisms:



The final pressure should be $3P_0$ (P_0 denotes the initial pressure of peroxide), both when ethane and when methane is the product of reaction.

The rate of decomposition was calculated on the assumption that the reaction obeys first-order kinetics and the computations were performed by the two methods:

- (a) Assuming $P_{final} = 3P_0$ (as required by the stoichiometry)
- (b) Assuming $P_{final} = 2.88P_0$

method (a) yielding rate constants higher than method (b).

The rate constants calculated by method (a) showed some fall-off towards the end of the run, while those calculated by method (b) were unchanged, and for this reason method (b) was used throughout the work. It was shown that the decomposition was a homogeneous gas reaction; that the first-order rate constant was not affected either by changes of the initial pressure of peroxide or by the addition of nitric oxide or propene; and that this rate constant was nearly the same when the decomposition was carried out in solution (142). It was concluded therefore that the observed rate of reaction measures the rate of initial decomposition of tertiary butyl peroxide into $(CH_3)_3CO \cdot$ radicals.

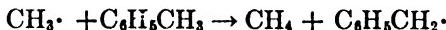
The activation energy was calculated at 39 kcal./mole from the temperature dependence of the rate constant, the relevant frequency factor being 3×10^{18} sec.⁻¹ Vaughan and his colleagues claimed therefore that

$$D[(CH_3)_3CO—OC(CH_3)_3] = 39 \text{ kcal./mole}$$

The above decomposition was reinvestigated recently by M. Szwarc and J. S. Roberts (198), who used a static method and added a great excess of toluene to the reacting mixture. The rate was measured by the rate of formation of $\text{CH}_4 + \text{C}_2\text{H}_6$, and the results indicated again that the reaction is homogeneous and obeys the first-order kinetics. The suggested mechanism is identical with that proposed by Vaughan:



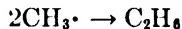
or



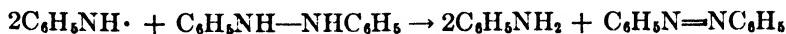
The values of rate constants were smaller by about a factor of 2 than those obtained by Vaughan, and the activation energy was estimated from the temperature dependence of the rate constant at 33-34 kcal./mole, the frequency factor being 1.5×10^{13} sec.⁻¹. On this basis a value of 33-34 kcal./mole was proposed for $D[(\text{CH}_3)_3\text{COOC}(\text{CH}_3)_3]$.

L. Various methods

The decomposition of mercury dialkyls has been investigated by E. Warhurst and G. B. Gowenlock (210). The technique was similar to that applied by E. T. Butler and M. Polanyi (35), and the extent of decomposition was measured by the rate of formation of mercury. It was demonstrated that the decomposition obeyed first-order kinetics. The activation energy was calculated by assuming the frequency factor to be 10^{13} sec.⁻¹. The following mechanism was suggested:

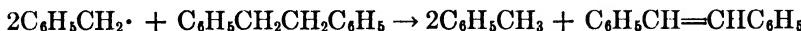


The decompositions of hydrazobenzene and phenylhydrazine have been investigated by M. J. S. Dewar (46). The decomposition was carried out in solution and the reaction was measured by the rate of disappearance of substrate. The reaction was proved to be of the first order, although the rate was dependent on the nature of solvent. The plot of $\log k$ against $1/T$ produced straight lines, and from their slopes the activation energies were estimated at 35-36 kcal./mole for hydrazobenzene and at about 48 kcal./mole for phenylhydrazine. The author suggests the following mechanism for these decompositions:

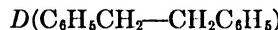


In conclusion, it is claimed that the observed activation energies measure the relevant N—N bond dissociation energies.

A similar mechanism was proposed by Miles (113) to account for the results of the pyrolysis of bibenzyl:



The pyrolysis was studied in the gas phase by means of a flow technique, and the rate was measured by the rate of formation of toluene. The activation energy was estimated at 45–48 kcal./mole and was identified with



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VI. APPENDIX

This appendix contains three types of tables:

1. *The tables of bond dissociation energies determined directly*

The values quoted (table A1) were taken from the literature without introducing any corrections. They contain the data obtained from direct observations and not those calculated from heats of formation of the respective compounds in conjunction with heats of formation of radicals determined either by independent methods or by some guesswork. The values favored by the writer and considered by him as reliable are given in heavier type. Those which seem uncertain are indicated by question marks.

The bond dissociation energies for diatomic molecules were omitted, since an excellent compilation of these data is found in A. G. Gaydon's recent monograph (*Dissociation Energies*, Chapman and Hall, London (1947)).

The bond dissociation energies for triatomic molecules were calculated on the basis of the corresponding values for $D(A-B)$ in the respective diatomic molecules. The values actually quoted were taken from recent papers by M. Wehrli and G. Milazzo (212) and by H. A. Skinner (164).

2. *The tables of heats of formation of radicals or atoms*

The values quoted in table A2 are computed on the basis of the respective bond dissociation energies. The values for the latter entities were either chosen from the literature or assumed on the basis of some observed regularities. It must be stressed, however, that in both cases the choice was a purely subjective one, reflecting the present opinion of the writer.

Every effort has been made to point out the assumptions on which these data are based, and the remarks added in the last column should help in this respect.

3. *The tables of "best" bond dissociation energies*

Assuming the heats of formation of radicals, as quoted in table A2, one may calculate the "best" bond dissociation energies (see table A3). This calculation requires a knowledge of the heats of formation of the respective compounds, and the data were taken from *Selected Values of Properties of Hydrocarbons*, or from the National Bureau of Standards monograph by F. R. Bichowsky and F. D. Rossini, or from modern publications. The references to the latter are given in a recent paper by J. S. Roberts and H. A. Skinner (150).

The values obtained in this way contain the uncertainties involved in the heats of formation of radicals (see Section IV,B) and in the estimation of the heats of formation of the respective compounds. The latter factor is of no significance in the case of hydrocarbons (and a few other compounds) for which modern and very accurate data are available.

The nature of the uncertainties is again stressed under the headings of the respective tables. The values determined directly are given in heavier type.

*Bond dissociation energies determined directly**Bond dissociation energies in teratomic molecules*

MOLECULE X—A—Y	<i>D(X—AY)</i>		METHOD	YEAR	INVESTIGATORS AND REFERENCES
	<i>kcal./mole</i>	<i>kcal./mole</i>			
H—O—H.....	115 ± 2.5 115 117 ± 1 114 ± 1 113.5 118 ± 0.7	115 ± 2.5 115 117 ± 1 114 ± 1 113.5 118 ± 0.7	2H ₂ O + O ₂ ⇌ 4OH Fluorescence Mercury-sensitized photolysis Explosion method 2H ₂ O + O ₂ ⇌ 4OH 2H ₂ O + O ₂ ⇌ 4OH	1928 1934 1934 1935 1937 1944	Bonhoeffer and Reichardt (25) Terenin <i>et al.</i> (203) Senftleben <i>et al.</i> (168) Lewis and von Elbe (102) Avramenko and Kondrat'ev (6) Dwyer and Oldenberg (50)
H—S—H.....	>78?	>78?	From <i>D(S—H)</i>		See Gaydon (80)
O—C—O.....	127	127	Thermochemistry		See Rossini <i>et al.</i> , <i>Selected Values of Properties of Hydrocarbons</i>
O—N—O.....	72	72	Thermochemistry		
Cl—N—O.....	37		2NO + Cl ₂ ⇌ 2NOCl	1939	Beeson and Yost (41)
Br—N—O.....	28		2NO + Br ₂ ⇌ 2NOBr	1934	Yost <i>et al.</i> (225)
O—N—N.....	39	?	Thermochemistry		
H—C—N.....	121?	?	Thermochemistry		
Cl—C—N.....	95?	?	Thermochemistry		
Br—C—N.....	83?	?	Thermochemistry		
I—C—N.....	71?	?	Thermochemistry		
Cl—Hg—Cl.....	80.5	80.5	Spectroscopic	1943	
Br—Hg—Br.....	71.5	71.5	Spectroscopic	1943	
I—Hg—I.....	57	57	Spectroscopic	1943	See Wieland (218) and Wehrli and Milazzo (212)
Cl—Hg—Br.....	77	70	Spectroscopic	1943	
Cl—Hg—I.....	74.5	62.5	Spectroscopic	1943	
Br—Hg—I.....	68	63.5	Spectroscopic	1943	

$\text{Cl}-\text{In}-\text{Cl}$	46	46	Based on spectroscopic $D(\text{In}-\text{Cl})$, $D(\text{In}-\text{Br})$, and $D(\text{In}-\text{I})$	1943	See Wehrli and Milazzo (212)
$\text{Br}-\text{In}-\text{Br}$	42	42		1943	
$\text{I}-\text{In}-\text{I}$	42	42		1943	
$\text{Cl}-\text{Ca}-\text{Cl}$	176?	176?		1949	
$\text{Cl}-\text{Mg}-\text{Cl}$	136 ± 20?	136 ± 20?	Using spectroscopic data for the corresponding dia- tomic molecules	1949	Computed by Skinner (164)
$\text{Cl}-\text{Be}-\text{Cl}$	147 ± 15	147 ± 15		1949	
$\text{Cl}-\text{Cd}-\text{Cl}$	84 ± 5?	84 ± 5?		1949	
$\text{Br}-\text{Cd}-\text{Br}$	76 ± 10?	76 ± 10?		1949	
$\text{I}-\text{Cd}-\text{I}$	57 ± 10	57 ± 10	Using spectroscopic data for the corresponding dia- tomic molecules	1949	See Wehrli and Milazzo (212)
$\text{Cl}-\text{Zn}-\text{Cl}$	96 ± 5?	96 ± 5?		1949	
$\text{I}-\text{Zn}-\text{I}$	53 ± 15?	53 ± 15?		1949	

Bond dissociation energies of some inorganic molecules

COMPOUND	D kcal./mole	METHOD	YEAR	INVESTIGATORS AND REFERENCES
$\text{HO}-\text{OH}$	54	From $D(\text{H}-\text{OH})$		
NH_3-H	<124	Predisociation	1928	Bonhoeffer and Farkas (24)
	<112	Mercury photosensitization	1935	Melville (111)
	<117	Fluorescence	1935	Terinin and Neumin (203)
	10 ⁴	$\text{NH}_3 + \text{H} \rightleftharpoons \text{NH}_2 + \text{H}_2$	1949	See Szwarc (192)
	$10^4 \pm 2$	Pyrolysis of hydrazine	1949	Szwarc (191)
	100	Pyrolysis of benzylamine	1949	Szwarc (192)
$\text{H}_2\text{N}-\text{NH}_2$	60 ± 4	Pyrolysis of hydrazine	1949	Szwarc (191)
$\text{O}_2\text{N}-\text{NO}_2$	13	$\text{N}_2\text{O}_4 \rightleftharpoons 2\text{NO}_2$	1897	Schreber (160)
	12.85	$\text{N}_2\text{O}_4 \rightleftharpoons 2\text{NO}_2$	1919	Wortzel (224)
	12.90	$\text{N}_2\text{O}_4 \rightleftharpoons 2\text{NO}_2$	1922	Bodenstein <i>et al.</i> (21)
	$14.5-14.7$	$\text{N}_2\text{O}_4 \rightleftharpoons 2\text{NO}_2$	1931	Verhoek and Daniels (207)
$\text{O}_2\text{N}-\text{NO}$	9.5		1929	Abel and Proisl (1)
	10	$\text{N}_2\text{O}_4 \rightleftharpoons \text{NO}_2 + \text{NO}$	1931	Verhoek and Daniels (207)

TABLE A1—Continued
Bond dissociation energies of hydrocarbons—I

TYPE C—H	D(C—H)	METHOD	YEAR	INVESTIGATORS AND REFERENCES
	kcal./mole			
C—H.....	80	Spectroscopic	1939	Herzberg (78)
CH ₃ —H.....	~98	Mirror technique (C ₂ H ₆)	1933	Rice and Dooley (143)
	100 ± 6	Mirror technique (CH ₄)	1934	Rice and Dooley (144)
	~103	Pyrolysis of CH ₄ I	1940	Polanyi <i>et al.</i> (11, 34, 35)
	101 ± 5	Electron impact	1942	Stevenson (177)
	~101	Electron impact	1942	Stevenson and Hippel (179)
	101 ± 1	Photobromination	1942	Kistiakowsky <i>et al.</i> (3, 4, 88)
	~101	Electron impact	1943	Stevenson (178)
	~101	Electron impact	1943	Hippel and Stevenson (83)
	103 ± 3	Pyrolysis of C ₄ H ₈ C ₂ H ₆ CH ₃ + H ₂ ⇌ CH ₄ + H	1949	Szwarc (189) See, for critical review, Wicke (217) and Steacie (168)
(CH≡C)—H.....	<121	Photodecomposition	1942	Cherton (39)
(CH ₂ =CH)—H.....	92?	Electron impact	1943	Stevenson (178)
CH ₃ CH ₂ —H.....	~102	C ₂ H ₆ + H ₂ ⇌ C ₂ H ₆ + H	1942	Computed by Wicke (217)
	~100	C ₂ H ₅ + H ₂ ⇌ C ₂ H ₆ + H	1946	Computed by Steacie (168)
	~97	Pyrolysis of C ₂ H ₆ I	1940	Polanyi <i>et al.</i> (11, 34, 35)
	~97	Electron impact	1943	Stevenson (178)
	~98	Photobromination	1944	Andersen and Van Artsdalen (5)
CH ₃ CH ₂ CH ₂ —H.....	~95	Pyrolysis of n-C ₃ H ₇ I	1940	Polanyi <i>et al.</i> (11, 34, 35)
(CH ₃) ₂ CH—H.....	89?	Pyrolysis of iso-C ₃ H ₇ I	1940	Polanyi <i>et al.</i> (11, 34, 35)
(CH ₂ =CHCH ₂)—H.....	~78	Pyrolysis of propene	1949	Szwarc (187)
	~77	Pyrolysis of 1-butene	1950	Szwarc and Sehon (199)

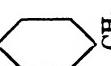
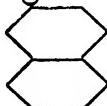
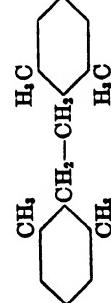
$n\text{-C}_3\text{H}_7\text{CH}_2\text{-H}$	~94	Pyrolysis of $n\text{-C}_3\text{H}_9\text{I}$	1940	Polanyi <i>et al.</i> (11, 34, 35)
$(\text{CH}_3)_2\text{C-H}$	86?	Pyrolysis of <i>tert</i> - $\text{C}_4\text{H}_9\text{I}$	1940	Polanyi <i>et al.</i> (11, 34, 35)
$[\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}_2]\text{-H}$	~76	Pyrolysis of 2-methylpropene	1949	Szwarc (188)
$\text{C}_4\text{H}_9\text{CH}_3\text{-H}$	77.6 ± 1.5	Pyrolysis of toluene	1947	Szwarc (183, 186)
	75 ± 1	Pyrolysis of <i>o</i> -xylene	1947	Szwarc (183, 186)
	77 ± 2	Pyrolysis of <i>m</i> -xylene	1947	Szwarc (183, 186)
	76 ± 1.5	Pyrolysis of <i>p</i> -xylene	1947	Szwarc (183, 186)
	76	Pyrolysis of α -methylnaphthalene	1950	Szwarc and Shaw (200)

TABLE A1—Continued
Bond dissociation energies of hydrocarbons—1—Continued

TYPE C—H	D/C—H kcal./mole)	METHOD	YEAR	INVESTIGATORS AND REFERENCES	
				Pyrolysis of β -methylnaphthalene	Ziegler <i>et al.</i> (228) Bent <i>et al.</i> (16)
	76	Pyrolysis of β -methylnaphthalene	1950	Szwarc ^a and Shaw (200)	
$(\text{C}_4\text{H}_9)_2\text{C—H}$	~75	Dissociation of $(\text{C}_4\text{H}_9)_2\text{CC}(\text{C}_4\text{H}_9)_2$	1929	Ziegler <i>et al.</i> (228) Bent <i>et al.</i> (16)	
Bond dissociation energies of hydrocarbons—2					
TYPE C—C	D(C—C) kcal./mole)	METHOD	YEAR	INVESTIGATORS AND REFERENCES	
				Rice and Dooley (143) See $D(\text{CH}_3, \text{—H})$	
$\text{CH}_3, \text{—CH}_3$	80 ± 6 82-87	Mirror technique Calculated from $D(\text{CH}_3, \text{—H})$	1933		
$(\text{CH}_3, \text{—CH}(\text{CH}_3), \text{—CH}_3)_2$	~61.5	Pyrolysis of 1-butene	1950	Szwarc and Sehon (199)	
$\text{C}_4\text{H}_9\text{CH}_3, \text{—CH}_3$	63 ± 1.5	Pyrolysis of $\text{C}_4\text{H}_9\text{C}_2\text{H}_5$,	1949	Szwarc (189)	
$\text{C}_4\text{H}_9\text{CH}_3, \text{—CH}_2\text{C}_2\text{H}_5$	47 45-48	Pyrolysis of toluene Pyrolysis of bibenzyl	1947 1949	Szwarc (184) Miles (113)	
	22?	Rate of thermal dissociation	1943	Coops <i>et al.</i> (42)	

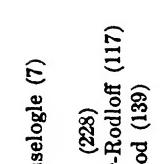
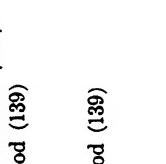
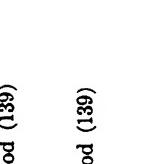
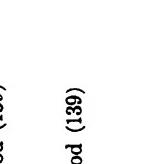
	CH ₃	H ₃ C	CH ₃ —CH ₂ —C(CH ₃) ₂	22?	Rate of thermal dissociation	1943	Coops <i>et al.</i> (42)
	CH ₃	H ₃ C	(H ₃ C) ₂ CH—CH—C(CH ₃) ₂	22?	Rate of thermal dissociation	1941	Coops <i>et al.</i> (41)
	CH ₃	H ₃ C	(H ₃ C) ₂ CH—CH—C(CH ₃) ₂	<28	Rate of thermal dissociation	1937	Bachmann and Wiselogle (7)
	CH ₃	H ₃ C	(C ₂ H ₅) ₂ C—CH(C ₂ H ₅) ₂	11 ± 1	Equilibrium constant	1929	Ziegler and Ewald (228)
	CH ₃	H ₃ C	(C ₂ H ₅) ₂ C—C(C ₂ H ₅) ₂	11.6 ± 2	Equilibrium constant	1935	Müller and Müller-Rodloff (117)
	CH ₃	H ₃ C	(C ₂ H ₅) ₂ C—C(C ₂ H ₅) ₂	10	Equilibrium constant	1941	Preckel and Selwood (139)
	CH ₃	H ₃ C	(C ₂ H ₅) ₂ C—C(C ₂ H ₅) ₂	11.4	Equilibrium constant	1941	Preckel and Selwood (139)
	CH ₃	H ₃ C	(C ₂ H ₅) ₂ C—C(C ₂ H ₅) ₂	11.5	Equilibrium constant	1941	Preckel and Selwood (139)

TABLE A1—Continued
Bond dissociation energies of hydrocarbons—3

TYPE C=C	D(C=C)	METHOD	YEAR	INVESTIGATORS AND REFERENCES
H ₂ C=CH ₂	kcal./mole	Predisociation in Schumann ultraviolet	1934	Price (140)
	<162	Predisociation in Schumann ultraviolet	1935	Hilgendorff (81)
	<159			

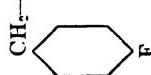
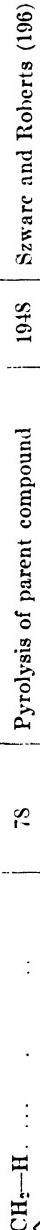
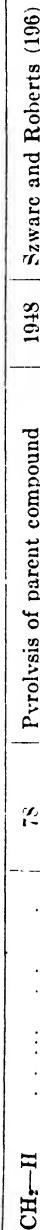
Bond dissociation energies of hydrocarbons—4

C≡C	D(C≡C)	METHOD	YEAR	INVESTIGATOR AND REFERENCE
HC≡CH.....	kcal./mole	Predisociation in Schumann ultraviolet	1934	Price (140)
	<187?			

Bond dissociation energies of halogen-substituted hydrocarbons—1

TYPE C—H	D(C—H)	METHOD	YEAR	INVESTIGATORS AND REFERENCES
CH ₂ Br—H.....	kcal./mole	Photobromination of CH ₂ Br	1942	Kistiakowsky and Van Artsdalen (88)
CCl ₄ —H.....	~99	Photochlorination of CCl ₄ H	1934	Schumacher and Wolff (161)
	~89	Photobromination of CCl ₃ H	1939	Braunwarth and Schumacher (27)
CBr ₃ —H.....	89 ± 2	Photobromination of CBr ₃ H	1939	Braunwarth and Schumacher (27)
CH ₂ F—H.....	93 ± 2	Pyrolysis of parent compound	1948	Szwarc and Roberts (106)
	78			





Bond dissociation energies of halogen-substituted hydrocarbons—2

TYPE C—Cl	$D(\text{C}-\text{Cl})$ kcal./mole	METHOD	YEAR	INVESTIGATORS AND REFERENCES	
				(74)?	Hot wire decomposition
CH_3-Cl	70				
CCl_3-Cl	≤ 70	$\text{CCl}_4 \rightarrow \text{Br}_2 \rightleftharpoons \text{CCl}_3\text{Br} + \text{BrCl}$	1949	Miller and Willard (unpublished results)	

Bond dissociation energies of halogen-substituted hydrocarbons—3

TYPE C—Br	$D(\text{C}-\text{Br})$ kcal./mole	METHOD	YEAR	INVESTIGATORS AND REFERENCES	
				Pyrolysis of CH_3Br	Pyrolysis of CF_3Br
CH_3-Br	~68		1949	Szwarc and Sehon (unpublished results)	
Cl_3-Br	~65		1949	Szwarc and Sehon (unpublished results)	
CCl_3Br	45?	Photooxidation of CCl_3Br	1939	Franke and Schumacher (58)	
	~52	Exchange Br_2 and CCl_3Br	1949	Miller and Willard (114)	
	~57	Exchange Br_2 and CCl_3Br	1949	Davidson and Sullivan (44)	

TABLE A1—Continued
Bond dissociation energies of halogen-substituted hydrocarbons—3—Continued

TYPE C—Br	$D(C-Br)$ kcal./mole	METHOD	YEAR	INVESTIGATORS AND REFERENCES	
(·CHClCHCl)—Br.....	11 ± 3	Bromination of CHCl=CHCl	1938	Müller and Schumacher (118)	
CHClBrCHCl—Br.....	51 ± 4	Bromination of CHCl=CHCl	1938	Müller and Schumacher (118)	
(·CH=CH)—Br.....	8 ± 4	Photobromination of acetylene	1939	Müller and Schumacher (119)	
(CH ₂ =CHCH ₂)—Br.....	48–50	Pyrolysis of allyl bromide	1949	Szwarc and Ghosh (194)	
	~45	Pyrolysis of allyl bromide	1949	MacColl (107)	
C ₆ H ₅ CH ₂ —Br.....	50 ± 2	Pyrolysis of benzyl bromide	1949	Szwarc and Ghosh (194)	

TYPE C—I	$D(C-I)$ kcal./mole	METHOD	YEAR	INVESTIGATORS AND REFERENCES	
CH ₂ I.....	~54	Pyrolysis of CH ₂ I	1940	Butler and Polanyi (34, 35)	
	<58	Absorption continuum	1937	Porret and Goodeve (138)	
CHCl ₂ —I.....	42?	Pyrolysis of CHCl ₂ I	1945	Polanyi <i>et al.</i> (33)	
CHBr ₂ —I.....	41?	Pyrolysis of CHBr ₂ I	1945	Polanyi <i>et al.</i> (33)	
CHI ₂ —I.....	37?	Pyrolysis of iodoform	1945	Polanyi <i>et al.</i> (33)	
C ₂ H ₅ —I.....	~52	Pyrolysis of C ₂ H ₅ I	1940	Butler and Polanyi (34, 35)	
	~51	Pyrolysis of C ₂ H ₅ I	1947	Szwarc (182)	
CH ₃ CICH ₂ —I.....	46?	Pyrolysis	1945	Polanyi <i>et al.</i> (33)	

$\text{CH}_3\text{ICH}_3-\text{I}$	<47	Photochemical decomposition	1930	Deduced from Schumacher and Wiig
$(\text{CH}_2=\text{CH})-\text{I}$	~55	Pyrolysis of vinyl iodide	1940	Butler and Polanyi (34, 35)
$n\text{-C}_4\text{H}_9-\text{I}$	~50	Pyrolysis of <i>n</i> -C ₄ H ₉ I	1940	Butler and Polanyi (34, 35)
$\text{Iso-C}_4\text{H}_9\text{I}$	~46	Pyrolysis of iso-C ₄ H ₉ I	1945	Polanyi, <i>et al.</i> (33)
$(\text{CH}_2=\text{CHCH}_3)-\text{I}$	39? 35-37	Pyrolysis of allyl iodide Pyrolysis of allyl iodide	1940 1948	Butler and Polanyi (34, 35) Szwarc and Shaw (163)
$n\text{-C}_6\text{H}_5-\text{I}$	~49	Pyrolysis of <i>n</i> -butyl iodide	1940	Butler and Polanyi (34, 35)
$(\text{CH}_3)_2\text{C}-\text{I}$	45?	Pyrolysis	1945	Polanyi, <i>et al.</i> (35)
Cyclo-C ₄ H ₉ -I	49?	Pyrolysis	1945	Polanyi, <i>et al.</i> (33)
$\text{C}_6\text{H}_5-\text{I}$	~54 >57	Pyrolysis of iodobenzene Pyrolysis of iodobenzene	1940 1947	Butler and Polanyi (35) Szwarc (182)
$\text{C}_6\text{H}_5\text{CH}_3-\text{I}$	44? ~39	Pyrolysis of benzyl iodide Pyrolysis of benzyl iodide	1940 1947	Butler and Polanyi (35) Szwarc (182)
$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_3-\text{I}$	50?	Pyrolysis	1945	Polanyi, <i>et al.</i> (33)

Bond dissociation energies of organic compounds containing oxygen—1

TYPE C—H	$D(\text{C}-\text{H})$ kcal./mole	METHOD	INVESTIGATORS AND REFERENCES	
			<78	>78
(HCO)—H		Threshold in photolysis	1939	Corin (67)
(CO)—H		Photolysis, temperature coefficient Photolysis	1939 1939	Corin (67) Remark by Style (180)

TABLE A1—Continued
Bond dissociation energies of organic compounds containing oxygen—2

TYPE C—C	$D(C-C)$ kcal./mole	METHOD	YEAR	INVESTIGATORS AND REFERENCES	
CH ₃ —CO	<10	Photolysis	1934	Leermakers (100)	
	<10	Photolysis	1936	Akeroyd and Norrish (2)	
	<17	Photolysis	1939	Gorin (67)	
	<18	Photolysis	1940	Herr and Noyes (77)	
	<9	Photolysis	1940	Grahame and Rollefson (69)	
	<9	Photolysis	1942	Blacet and Loeffler (20)	
	<15	Photolysis	1943	Benson and Forbes (15)	
CH ₃ —CHO	75 ± 2	Photolysis	1940	Grahame and Rollefson (69)	
CH ₃ CO—COCH ₃	60	Pyrolysis of biacetyl	1950	Szwarc and Murawski (195)	
	<64	Threshold in photolysis	1952	Anderson and Rollefson (5a)	
C ₆ H ₅ CH ₂ —COCH ₃	63	Pyrolysis of C ₆ H ₅ CH ₂ COCH ₃	1950	Szwarc and Murawski (195)	

Bond dissociation energies of organic compounds containing oxygen—3

TYPE O—O	$D(O-O)$ kcal./mole	METHOD	YEAR	INVESTIGATORS AND REFERENCES	
C ₂ H ₅ O—OC ₂ H ₅	~30	Pyrolysis	1938	Harris and Egerton (72)	
C ₂ H ₅ O—OC ₃ H ₇	~35	Pyrolysis	1939	Harris (71)	
(CH ₃) ₂ CO—OC(CH ₃) ₃	39	Pyrolysis	1948	Rust, Vaughan, <i>et al.</i> (141)	
	34	Pyrolysis	1950	Szwarc and Robertis (198)	
CH ₃ COO—OCOCH ₃	~30	Pyrolysis	1937	Walker and Wild (209)	

$\text{C}_6\text{H}_5\text{COO}-\text{OCOC}_6\text{H}_5$	~30	Thermal decomposition in solution	1940	Kamenskaya and Medvedev (86)
		30-33	Thermal decomposition in solution	1946	Nozaki and Bartlett (121)
		28-30	Thermal decomposition in solution	1947	Hartman, Sellers, and Turnbull (74)
		~27.5	Thermal decomposition in solution	1948	Brown (30)
		~30	Thermal decomposition in solution	1949	Bawn <i>et al.</i> (13)

Bond dissociation energies of organic compounds containing oxygen—4

TYPE C—O	$D(\text{C}-\text{O})$	METHOD		YEAR	INVESTIGATORS AND REFERENCES
		kcal./mole		
CH_3-OH	~90	Fluorescence	1934	Terenin <i>et al.</i> (203)
$\text{C}_2\text{H}_5-\text{OH}$	~90	Fluorescence	1934	Terenin <i>et al.</i> (203)
$\text{HCO}-\text{OH}$	~90?	Fluorescence	1934	Terenin <i>et al.</i> (203)
$\text{CH}_3\text{CO}-\text{OH}$	~90?	Fluorescence	1934	Terenin <i>et al.</i> (203)

Bond dissociation energies of organic compounds containing nitrogen—I

TYPE C—H	$D(\text{C}-\text{H})$	METHOD		YEAR	INVESTIGATORS AND REFERENCES
		kcal./mole		
 CH_2-H	75	Pyrolysis	1948	Roberts and Szwarc (151)
 CH_2-H	76	Pyrolysis	1948	Roberts and Szwarc (151)
 CH_2-H	77	Pyrolysis	1948	Roberts and Szwarc (151)

TABLE A1—*Concluded*
Bond dissociation energies of organic compounds containing nitrogen—2

TYPE C—C	$D(C-C)$ kcal./mole	METHOD	YEAR	INVESTIGATORS AND REFERENCES	
				Predisociation	Pyrolysis
NC—CN	~100	Predisociation	1932	Hogness and Ts'ai (84)	
	77?	Pyrolysis	1933	Kistiakovsky and Gershinowitz (87)	
	146?	Pyrolysis	1940	White (216)	
	<127	H ₂ + (CN) ₂ ⇌ 2HCN	1942	Robertson and Pease (153)	
	117-120	Lattice energy	1948	Glockler (66)	
CH ₃ —CN	~105?	Fluorescence	1934	Terenin <i>et al.</i> (203)	

Bond dissociation energies of organic compounds containing nitrogen—3

TYPE C—N	$D(C-N)$ kcal./mole	METHOD	YEAR	INVESTIGATOR AND REFERENCE	
				59 ± 4	Pyrolysis
C ₆ H ₅ CH ₃ —NH ₂					

Bond dissociation energies of organic compounds containing nitrogen—4

TYPE N—N	$D(N-N)$ kcal./mole	METHOD	YEAR	INVESTIGATOR AND REFERENCE	
				~48	Thermal decomposition in solution
C ₆ H ₅ NH—NH ₂					
C ₆ H ₅ NH—NHC ₆ H ₅	~35	Thermal decomposition in solution	1950	Dewar (46)	

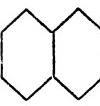
TABLE A2

Heats of formation of radicals or atoms in the gaseous state from elements in their standard states

RADICAL OR ATOM	ΔH_f° kcal./mole	METHOD	REMARKS
H.....	+52.0	Spectroscopic	Rossini <i>et al.</i> , <i>Selected Values of Properties of Hydrocarbons</i> (1948)
Cl.....	+29.0	Spectroscopic	
Br.....	+26.7	Spectroscopic	
I.....	+25.5	Spectroscopic	
O.....	+59.2	Spectroscopic	
OH.....	+10.0	$2\text{H}_2\text{O} + \text{O}_2 \rightleftharpoons 4\text{OH}$	
CN.....	+100 ?	$(\text{CN})_2 \rightleftharpoons 2\text{CN}; D(\text{CN}-\text{CN}) = 127 \text{ kcal./mole}$	
NO.....	+21.5	Calorimetric	
NH ₂	+41 ± 2	Pyrolysis of hydrazine	
NO ₂	+7.4	Calorimetric	
CH ₃	+31 ± 1	Photobromination	Well established
CHO.....	0 ?	Decomposition of ClIO	Very unreliable
C ₂ H ₅	+26 ± 2	Photobromination	Might be slightly higher
C ₂ H ₅ O.....	-10 ?	Pyrolysis of C ₂ H ₅ ONO	Very unreliable; leads to $D(\text{C}_2\text{H}_5\text{O}-\text{C}_2\text{H}_5) < D(\text{C}_2\text{H}_5-\text{O})$
CH ₂ =CH.....	+64 ?	Estimate	$D[(\text{CH}_2=\text{CH})-\text{H}]$ seems to be $> D(\text{CH}_3-\text{H})$
CH≡C.....	+123 ?	Photodecomposition	Very uncertain
CH ₃ CO.....	-4 to 8	Pyrolysis of biacetyl	Lack of modern combustion data
n-C ₃ H ₇	+18 ?	Pyrolysis of n-C ₃ H ₇ I	Uncertain
Iso-C ₃ H ₇	+12 ?	Pyrolysis of iso-C ₃ H ₇ I	Uncertain
CH ₂ =CHCH ₂	+ 29.5 ± 2	Pyrolysis of 1-butene	Cross-checks: pyrolysis of propene and allyl bromide
CH ₂ =C(CH ₃)CH ₂	+20 ?	Pyrolysis of 2-methylpropene	
n-C ₄ H ₉	+12 ?	Pyrolysis of n-C ₄ H ₉ I	
(CH ₃) ₂ C.....	+3 ?	Pyrolysis of <i>tert</i> -C ₄ H ₉ I	Very uncertain
C ₄ H ₈	+72 ?	Estimate	$D(\text{C}_4\text{H}_8-\text{H})$ seems to be $> D(\text{CH}-\text{H})$
C ₄ H ₈ CH ₂	+37.5 ± 1.5	Pyrolysis of toluene	Cross-checks: pyrolysis of C ₆ H ₆ , C ₂ H ₆ , and C ₄ H ₈ CH ₂ Br

TABLE A3
R'-R" bond dissociation energies
Hydrocarbons

For uncertainties in $D(R'-R'')$ compare the table of ΔH_f of respective radicals
 The bond dissociation energies estimated directly are set in heavy type

R'	R''	H	CH_3	C_2H_5	$CH_2=CH$	$CH \equiv C$	$*-C_2H_5$	$iso-C_2H_5$	$CH_2=CHCH_3$	$*-C_3H_8$	$tert-C_4H_9$	C_6H_5	$C_6H_5CH_3$
CH_3	101	83	82	90?	110?	79	74.5?	60	78	74?	91?	63	
C_2H_5	98	82	82	90?	109?	79	75?	60.5	78	73?	91?	62	
$CH_2=CH$	104?	90?	90?	101?			87?	85?	68.5?	86?	81?	101?	
$CH \equiv C$	121?	110?	109?			106?	103?					119?	
$n-C_4H_9$	95	79	79	87?	106?	76	72?	57.5	75	70?	88?	59	
Iso- C_4H_9	89?	74.5?	75?	85?	103?	72?	66.5?	54.5?	71?	65?	83?	54.5?	
$CH_2=CHCH_2$	77	60	60.5	68.5?			57.5	54.5?	38	56.5			
$n-C_4H_9$, (CH ₃) ₂ C.....	94	78	78	86?			75	71?	56.5	74	69?	87?	57.5
$CH_2=C(CH_3)CH_2$	76?	60?	60?				70?	65?		69?	60?	78?	
C_6H_6	104?	91?	91?	101?	119?	88?	83?			87?	78?	103?	76.5?
$C_6H_5CH_2$	77.5	63	62				59	54.5?		57.5		76.5?	47
$o-CH_3C_6H_4CH_2$	74	58	58										
$m-CH_3C_6H_4CH_2$	77.5	62	62.5										
$p-CH_3C_6H_4CH_2$	75	60	60										
CH_2		~76											
													
		~76											

R'-R" bond dissociation energies

For uncertainties in $D(R'-R'')$ see the table of ΔH_f of respective radicals
 The bond dissociation energies estimated directly are set in heavy type
 The values of $D(R'-R'')$ calculated on the basis of ΔH_f of the respective compounds are denoted by an asterisk if the ΔH_f is uncertain

R'	R''	H	Cl	Br	I	OH	NH ₂	CN	CHO	COCH ₃	NO ₂	NO
CH_3	101	80	66-67	64-55	91 (90)	79		110? (105)	71-75	77?	57	
C_2H_5	98	80	65	51-52	93 (90)	78			71?	77?	52	
$n-C_4H_9$	95	77*		50	92	77*			71?	77?		
(CH ₃) ₂ CH.....	89?		85?	75?	61?	~46	~90			73?		
(CH ₃) ₃ C.....												
$CH_2=CH$	104?	86?		65?					121?	84*?		
$CH_2=CHCH_2$	77	58	48	35-37	71		61*		92*?	50?		
C_6H_6	104?	88?		57?	107*?		94*?		124*?	83*?		
$C_6H_5CH_2$	77.5	50.5	39?		73*	69		95*?		63		
CHO.....	79?					96? (90)	89?			59?	59?	
CH_3CO	85?	82?	67?	51?	102? (90)	98?			59?	60		

It is necessary to acknowledge the existence of three previous communications attempting to systematize the data concerned with bond dissociation energies: a review by E. Wicke (217) published in 1942; a monograph by E. W. R. Steacie (168) published in 1946; and an extensive compilation by J. S. Roberts and H. A. Skinner (150) published in 1949. The data given in the present paper differ only slightly from those recommended by Roberts and Skinner. It seems, however, that Roberts and Skinner reported the various bond dissociation energies and heats of formation of radicals with an accuracy which is not warranted by the actual accuracy of the experimental determinations. They put the whole emphasis on the accuracy of thermochemical data used in their calculations, stressing to a lesser extent the uncertainties in the bond dissociation energies measured directly and consequently in the heats of formation of the radicals.

THE ABSORPTION SPECTRA OF CHLOROPHYLL AND RELATED COMPOUNDS¹

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The absorption spectra of chlorophyll and homologous compounds are described qualitatively. Included are brief discussions of the contribution of polar species to the ground state, the influence of the spatial orientation of the substituent on the spectra, chelate and acid *vs.* free-base spectra, fluorescence and phosphorescence, and the initial contemporary analyses of the band structure.

Absorption spectra have been the most prominent of the physical properties used for analysis of the so-called "fine" structure of porphyrins,² including chlorophyll, and involve such questions as hydrogen isomerism in the porphyrins, nitrogen equivalence of the pyrrole rings, and the arrangement of the double bonds in a typical porphyrin such as chlorophyll. An appreciation of the absorption spectra of the chlorophylls is obtained by comparing them with homologous compounds and with derivatives. This review does not attempt to list all the diverse phenomena and data in this field; rather, a selection has been made of certain absorption spectra studies which appear to be of most significance.

Physical characteristics, such as high melting points and sharpness of absorption bands, and organochemical characteristics, such as substitution rather than addition reactions, unusual stability of the metal chelates, etc., have long ago attested to the "aromatic" character of the porphyrin nucleus. Although the Kekulé type of resonance, as exemplified in benzene and homologs, is assumed by most workers in this field,³ later studies (2, 14) pointed out the contribution

¹ Contribution No. 91 from the Institute for Atomic Research and Department of Botany, Iowa State College, Ames, Iowa.

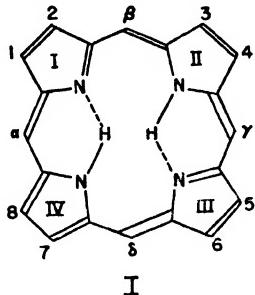
This work was done, in part, in the Ames Laboratory, Atomic Energy Commission.

² The term "porphyrins" is used to denote all tetrapyrrolic compounds in which the rings are linked by methine carbons in a closed conjugated system. Porphyrins are then subdivided into porphines and chlorines; in the former *none* of the β - or β' -carbons within the rings are reduced, while in the latter, two adjacent carbons (β, β') are thus reduced. Phorbines are a type of chlorine in which an isoecyclic ring (carbons 9 and 10) joining C₇ and C₈ is present. Phorbides are chlorines (or phorbines) in which the carbon substituent on C₇ is in a state of oxidation higher than methyl.

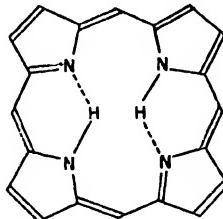
The names "porphin," "chlorin," and "phorbin" appear in much of the literature dealing with these compounds; however, in 1946 *Chemical Abstracts* adopted the "ine" ending, which is therefore used throughout this paper.

³ A notable exception was H. Fischer and his school. For their arguments, which rely primarily on spectral data, see below. In a variety of cases, of which porphyrins are only a prominent example, the question arises as to the mobility of hydrogen in the hydrogen bond. If mesomeric forms occur in which the movement is over a large distance, we term them tautomers. The two tautomers are distinct compounds, often of sufficient differences of energy so that they can be separated physically. If we can write different forms in which there is no movement of the hydrogen, we denote these as structures which contribute to the resonance. If the distance over which the hydrogens can move is so small that separation of the tautomers is improbable because of small energy differences, then we can conceive of a

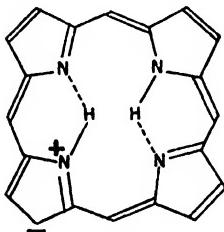
of dipolar and tetrapolar species to the total structure. A pair of Kekulé resonance structures is depicted by skeletal formulas I and II, while examples of dipolar and tetrapolar species are given in III, IV, and V.



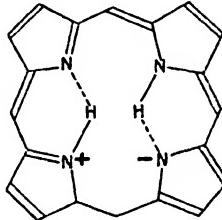
I



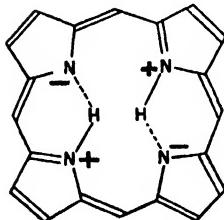
II



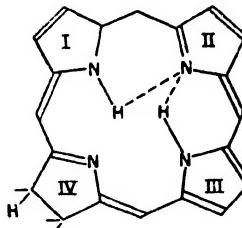
III



IV



V

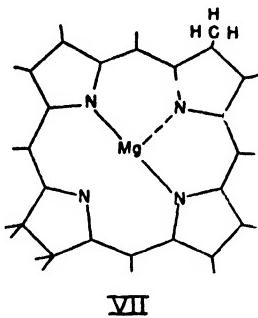


VI

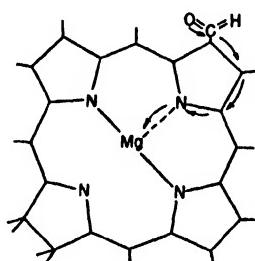
difficulty in distinction between a tautomer and a resonance form. [Although claim has actually been made of the preparation of porphine tautomers (P. Rothmund: J. Am. Chem. Soc. **58**, 625 (1936); **61**, 2912 (1939)), this was shown to be incorrect (S. Aronoff and M. Calvin: J. Org. Chem. **8**, 205 (1943); M. Calvin, R. H. Ball, and S. Aronoff: J. Am. Chem. Soc. **65**, 2259 (1943))]. A true distinction between tautomerism and resonance in this instance is made by Erdman and Corwin (10), although their evidence is not conclusive (see text and accompanying footnote). It was therein concluded that "a hydrogen atom in a porphyrin ring is bonded to a single nitrogen atom at any instant *even though it may be within the field of force of the adjacent nitrogen at the time.* . . . This does not mean that stable opposite and adjacent isomers necessarily exist but simply that the hydrogens remain fixed to specific individual nitrogens for periods of time exceeding the period of existence of an excited form." (Italics, S. A.) In the text no distinction is drawn between such tautomers with extremely low energy requirements for interconversion and the identically depicted resonance-contributing forms.

The change in the spectral type on substitution in the porphine ring was associated by Haurowitz *et al.* (14) with the predominance of different ionic species. The substitution of a relatively electropositive alkyl group for hydrogen tends to cause the contribution of species such as III (above) to be more prominent. This probably affords the beginning of an explanation of the effect on the absorption spectra of "adjacent" and "opposite" substitution (see below).

The structure of a chlorine (VI), although bearing some analogies to the above, is not completely analogous, for the nitrogens are no longer equivalent, i.e., the probability of the nitrogen of ring IV forming a homopolar bond with the internal hydrogens is small. Although the homopolar type of resonance occurs, the dipolar type is strongly diminished, the contribution of the nitrogen of ring IV being reduced to a minimum. This relationship may be of importance, e.g., in explaining the difference in the rates of hydrolysis of magnesium from chlorophylls a and b (23, 24), where it has been found that pheophytin a is formed about eight times as rapidly as pheophytin b. The magnesium of chlorines is undoubtedly not held as strongly as that of porphines; according to the above reasoning it would have only a tripole instead of quadripole coördination.



VII



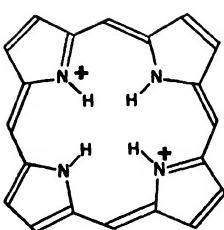
VIII

Schematic for chlorophyll a⁴Schematic for chlorophyll b⁴

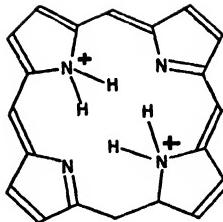
Consequently the effect of an electronegative chromophore, as present in the 2-formyl group of chlorophyll b, in direct conjugation with a pyrrole nitrogen, which would tend to make the magnesium-nitrogen bond stronger, would in turn decrease the rate of hydrolysis. A similar problem, though more difficult and obscure, is presented in the different rates of the phase test undergone by the two chlorophylls.

The porphines, generally forming disalts, exhibit characteristic changes in spectrum from the four-banded to a two-banded spectrum. The general structures must be as given in formula IX and/or formula X.

⁴ The formulas as indicated are not intended to denote homopolar bonding. Although exchange experiments with radioactive Mg⁺⁺ and purified chlorophylls were negative (S. Ruben, A. W. Frenkel, and M. D. Kamen: J. Phys. Chem. **46**, 710-14 (1942)), they may well be interpreted as in the corresponding negative experiments of radio-Fe⁺⁺ and ferrihemin (S. Ruben, M. D. Kamen, M. B. Allen, and P. Nahinsky: J. Am. Chem. Soc. **64**, 2297 (1942)) —a lack of exchange because of spatial hindrance. The ionic nature of the magnesium bonding is not, however, proved.



IX



X

The typical free base porphyrin generally displays four main bands in the visible (with occasional secondaries) and a primary band in the near ultraviolet.

The bands in the visible are usually numbered I, II, III, IV, beginning with the longest wave lengths. Among the twenty-four possible types of spectra (that is, with varying degrees of prominence of bands) only three occur naturally in the porphines, while a fourth is found in the chlorines (see figure 1). The etio

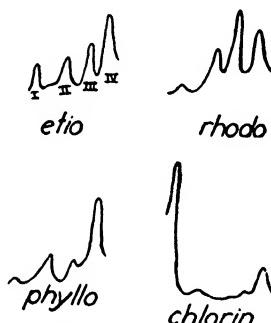


FIG. 1. Types of porphyrin spectra (from Fischer and Orth (11))

type is characteristic not only of the etioporphines, but of the majority of porphine spectra. We may speculate that deviations from this type of spectra occur only when substitutions in the pyrrole rings cause the density distribution of π -electrons to lie more on one half of the ring than the other (e.g., compare the diethyldimethylporphines in figure 2).⁵ This statement will be discussed in somewhat greater detail below. The etio-type spectrum thus occurs in such divergently substituted materials as the monosubstituted etioporphines, the tetramethyl-, tetraethyl-, and octamethyl-porphines, and tetramethylporphine-tetrapropionic acid. It is therefore a distinct surprise to note that the spectrum of porphine itself (figure 3) is of the phyllo type, which normally results either from a substitution within the ring itself, i.e., on a methine carbon as in phyllo-porphine or by "adjacent" rather than the "opposite" substitutions. The meth-

⁵ An exception to this generalization appears to exist in the spectra of the dibromodeuteroetioporphines II (2,6-dibromo) and III (2,3-dibromo) (35). In this instance the 2,6-dibromo compound appears to result in a rhodo-type spectrum, while the 2,3-dibromo-porphine results in an etio-type spectrum. These data appear, however, to be at variance with the qualitative descriptions of the spectra of the same compounds (11).

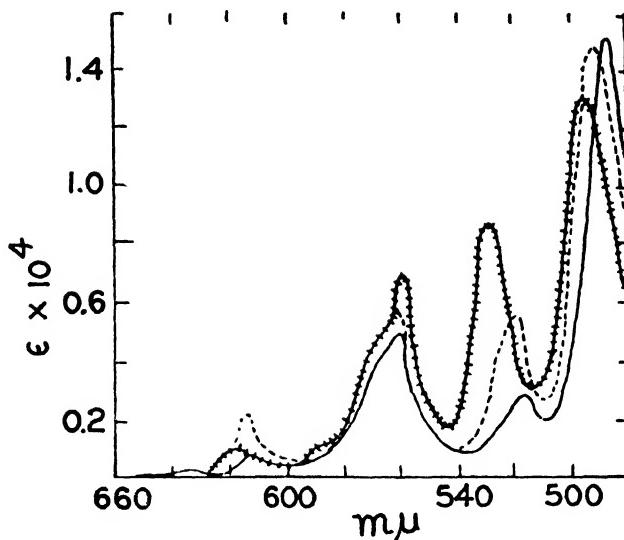


FIG. 2. The similarity of absorption spectra of porphine isomers (from Stern, Wenderlein, and Molvig (40)). —, porphine; - - -, 1,4-diethyl-2,3-dimethylporphine in dioxane; +++, 2,6-diethyl-1,5-dimethylporphine in dioxane.

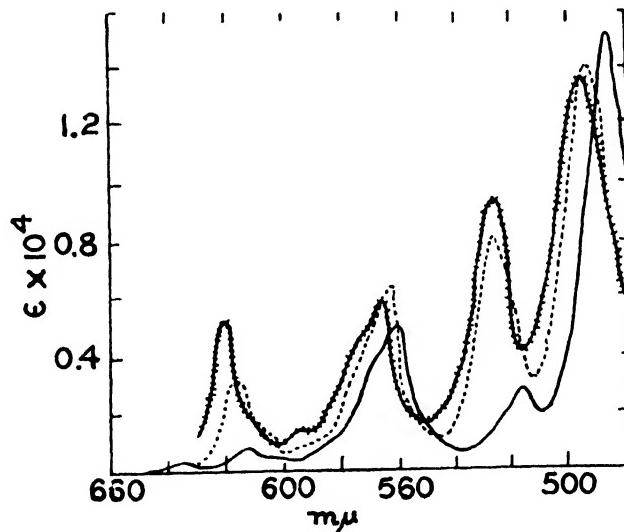


FIG. 3. The abnormality of the absorption spectrum of porphine (from Stern, Wenderlein, and Molvig (40)). —, porphine; +++, etioporphine I; - - -, deuterioetioporphine II (3-free).

ods of synthesis of porphine in this instance are by no means unequivocal, and the question thus arises as to whether "porphine" may not be a mixture of materials, as was shown to be the case in a similar type of synthesis (1), resulting

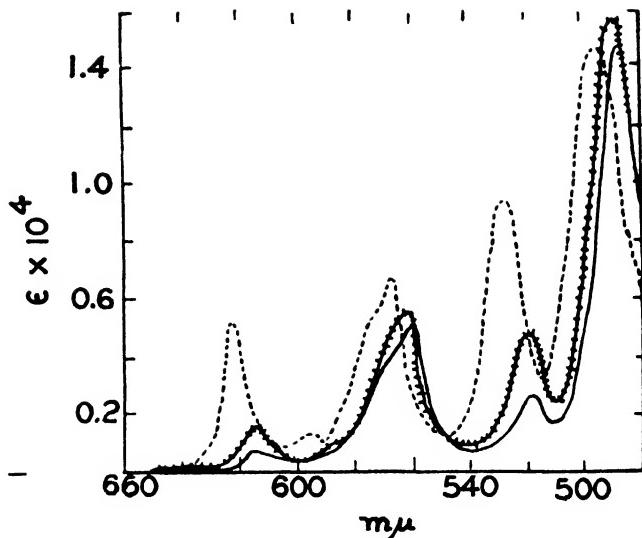


FIG. 4. The phyllo-type spectrum, resulting from "adjacent" substitutions (from Stern, Wenderlein, and Molvig (40)). —, porphine; +++, methyl ester of porphine-1,4-dipropionic acid; ---, tetramethyl ester of coproporphyrin II.

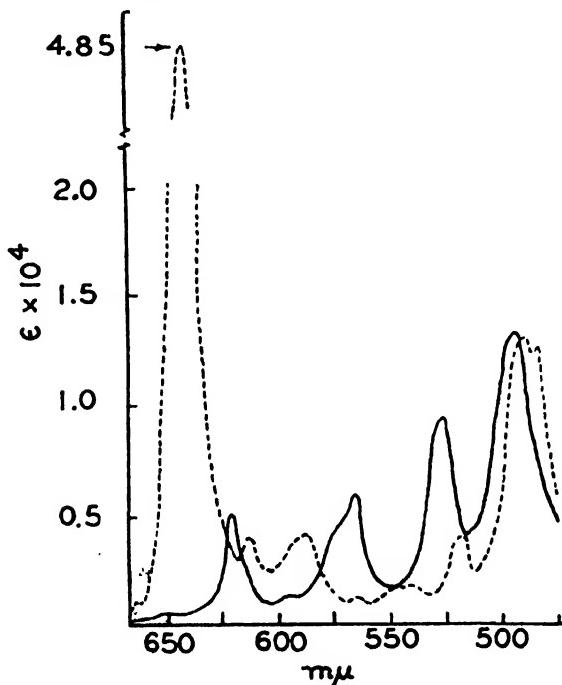


FIG. 5. Absorption spectra of homologous chlorines and porphines (from Pruckner (28)). —, etioporphine I; ---, etiochlorine I.

not only in the methine-substituted porphine, $\alpha, \beta, \gamma, \delta$ -tetraphenylporphine, but its chlorine and at least four other substances also showing porphyrin spectra. The rhodo-type spectrum, like the phyllo, results from "adjacent" substitutions. Thus, e.g., in rhodoporphine (XV) itself, or as in figure 4 in the dimethyl ester of porphine-1,4-dipropionic acid, a rhodo-type spectrum results, while in the tetramethyl ester of the symmetrical porphinetetrapropionic acid, coproporphine

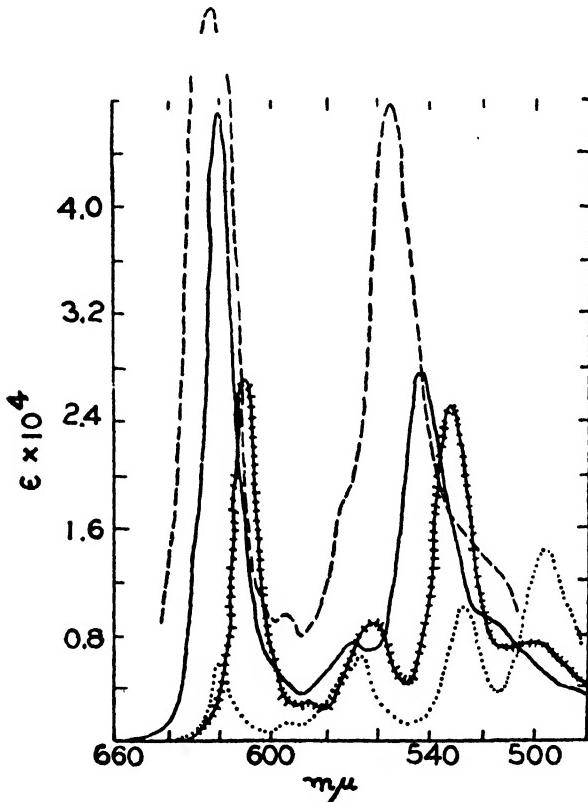


FIG. 6. Absorption spectra of imidoporphines (from Stern and Pruckner (37)). —, β, δ -diimidoetioporphine II; +++, monoimidoetioporphine II; . . ., etioporphine II; - - -, tetraimidoetioporphine.

II, an etio type results. A typical chlorine spectrum, in contrast to the corresponding porphine spectrum, is shown in figure 5.

That a difference in spectra should occur when substitutions are "adjacent" or "opposite" has been used by Fischer (*loc. cit.*) as an argument against the equivalence of the nitrogens in porphines and for the presence of both pyrrole and pyrrolin rings. This argument could be used with equal facility in another closed conjugated system such as benzene, where, e.g., *m*-dinitrobenzene would be expected, with this reasoning, to have a spectrum identical with that of *o*-dinitrobenzene. A difference in symmetry relationships, however, can result in

considerably different spectra, and a similar situation should be found in the porphines.

The substitution of nitrogen for a methine carbon (as in the phthalocyanines) yields a polybanded spectrum (figure 6) considerably different from the porphine type. The intense predominance of two of the four bands, occurring even in the monoimidoporphines, is more apparent in the diimidoporphines and most apparent in the tetraimidoporphines. These differences are emphasized by the increasing absorption coefficients, which are proportional to the number of nitrogens substituted. For example, for the mono-, di-, and tetra-imido compounds, the molar extinction coefficients of the primary red band are, respectively, 2.8

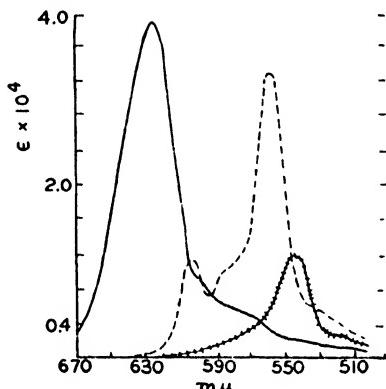


FIG. 7

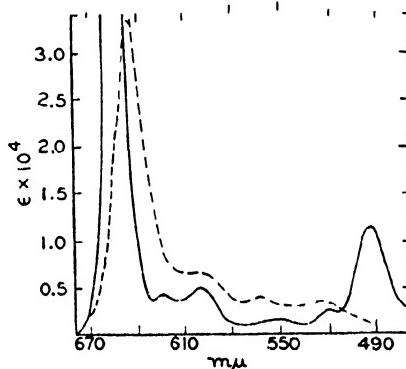


FIG. 8

Fig. 7. Acid spectra of porphines (from Stern and Pruckner (37)). —, tetramethyl ester of coproporphyrin II in 3 N hydrochloric acid; ---, tetramethyl ester of β,β -dimimidocoproporphyrin II in 6 N hydrochloric acid; +++, porphine in 6 N hydrochloric acid.

Fig. 8. Acid spectra of chlorines (from Stern and Molvig (36)). —, dimethyl ester of mesorhodochlorine in dioxane; - - -, dimethyl ester of mesorhodochlorine in aqueous hydrochloric acid.

$\times 10^4$, 4.8×10^4 , and (by extrapolation) 9.5×10^4 . (A triimidoporphine has not yet been synthesized.)

Inasmuch as the porphines are bases in which the basic atoms participate strongly in the excited state, their spectra might be expected to vary with the acidity. Typical acid spectra are shown in figures 7 and 8. Since porphines are generally dibasic (8), it might be expected that spectroscopic investigation of the course of titration of a porphine would reveal the existence of two acid spectra (2). Such is apparently not the case, intermediate spectra appearing to be capable of calculation from the spectra of the free base and the disalt. It is concluded that if the monosalt exists, it does so only over a very short range. Of unique interest is the similarity of the spectra of divalent metal chelates and disalt spectra (10), which also have full equivalence structurally (see figure 9).

One of the more spectacular achievements in porphyrin chemistry was the synthesis of *N*-alkylporphyrins (10, 21). The synthesis of these compounds was performed in an attempt to settle the question of whether a hydrogen isomerism

(i.e., a tautomerism) existed, or whether the hydrogens were essentially static and only resonance occurred. It was reasoned that if an *N*-substituted porphine could be synthesized, this substituted nitrogen would not be able to partake in resonance, and the spectrum should be significantly different from that of the normal porphine, e.g., the etio-type spectrum. It might, for example, be similar to that of a chlorine, although in one case the path of the π -electrons would include nitrogen and in the other the β -carbon atoms. It should, at any event, destroy the equivalence of the nitrogens. As shown in figure 10, the absorption spectrum of the free base of *N*-methyletioporphine was very similar to that of the normal bases, though shifted somewhat to the red. The conclusion was there-

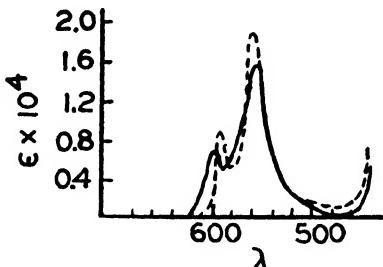


FIG. 9

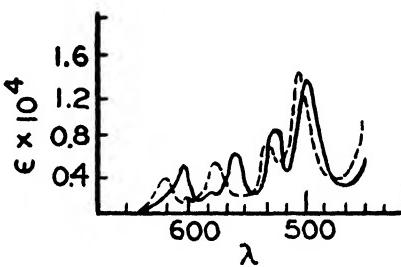
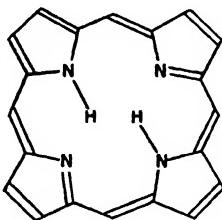


FIG. 10

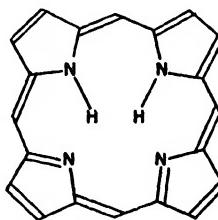
FIG. 9. Equivalence of salt and monovalent metal spectra of porphines (from Erdman and Corwin (10)). —, etioporphine II dihydrochloride; - - -, disodium salt of etioporphine II.

FIG. 10. Similarity of normal and *N*-methylporphines (from Erdman and Corwin (10)). —, etioporphine II; - - -, *N*-methyletioporphine II.

fore reached that tautomerism, rather than resonance, exists in normal porphines, with a very low energy barrier between, e.g., tautomers XI and XII. More specifically, the life of the tautomers is greater than the life of the excited (singlet) state (10).⁶



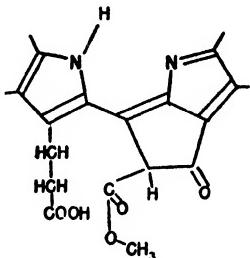
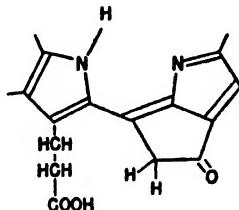
XI



XII

⁶ It should be pointed out that even in *N*-methylporphines the Kekulé resonance remains, as does the contribution of the ionic forms. Only tautomerism is partially restricted. Furthermore, since the nitrogens are equivalent, the remaining hydrogen is still mobile and tautomerism is still possible. True restriction could occur only if the nitrogens were not equivalent, as in chlorines, or if a di(*N*-methyl)porphine rather than an *N*-methyl, were considered. To some extent this is realized in comparing the metal chelates of the chlorines (see figure 15), which are essentially single-banded, with the corresponding chelates of porphines (figures 12, 13, 14), which are doubly banded.

Numerous instances have been observed in which structural relationships would be expected by analogy to be observed in spectra, but which do not exist. Thus, the dimethyl ester of pheophorphine a_5 should exhibit a spectrum very

Pheophorphine a_5 

Phylloerythrine

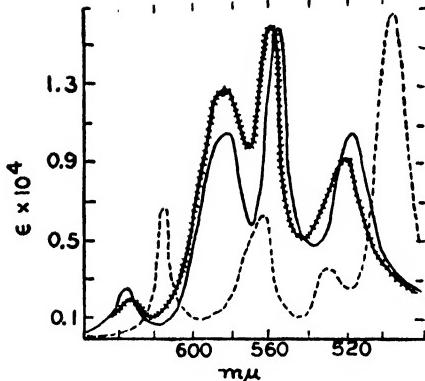


FIG. 11

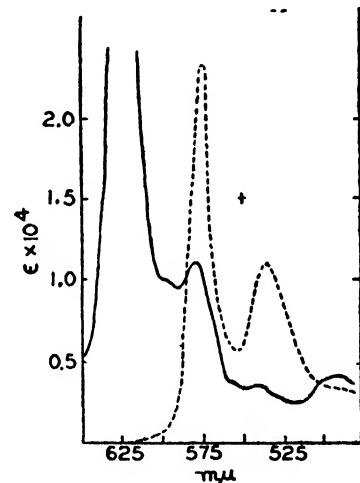


FIG. 12

FIG. 11. Influence of C_{10} substituents on absorption spectra (from Stern (34)). ---, dimethyl ester of pheophorphine a_5 ; —, monomethyl ester of phylloerythrine; +++, monomethyl ester of desoxophylloerythrine.

FIG. 12. Absorption spectra of metal chelates of corresponding porphines and chlorines (from Pruckner (28)). —, copper salt of dimethyl ester of mesorhodochlorine; ---, copper salt of dimethyl ester of rhodoporphyrine.

similar to that of phylloerythrine, but it does not do so (figure 11). On the contrary, that of desoxophylloerythrine, which might be expected to differ exceedingly from phylloerythrine (because of enolization and other influences), does not. Profound differences, however, do occur in strong acid (2), as would be expected in oxonium-ion formation.

Outstanding among the properties of the porphyrins is the ability to chelate with metals. All classes of metals form porphyrin complexes, which, however, vary considerably in the strength of chelation (and undoubtedly bond type).

Thus, the alkali and the alkaline earth metals are readily removed from porphyrins by acid, substances like zinc are less so, transition metals like iron only with difficulty, while the copper chelates are stable even in concentrated sulfuric acid. The spectra of the synthetic copper and zinc tetraphenylporphines and chlorines (7) indicate similar wave lengths (actually increasing with increasing weight of metal) but with significant differences in numerical value of the absorption coefficient (26). Metal chelates of the chlorines appear to possess a more complex spectrum than the corresponding porphine (see figure 12). Although spectra of copper chelates of porphines are generally two-banded, as compared to their singly banded chlorines (see figures 12, 13, 14), this type of generaliza-

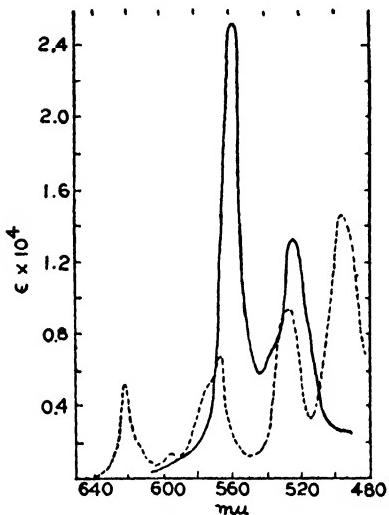


FIG. 13

FIG. 13. Absorption spectra of a typical porphine and its copper chelate (from Stern, Wenderlein, and Molvig (40)). —, copper salt of tetramethyl ester of coproporphine II; ---, tetramethyl ester of coproporphine II.

FIG. 14. Absorption spectra of porphine and its copper chelate (from Stern, Wenderlein, and Molvig (40)). —, porphine; ---, copper salt of porphine.

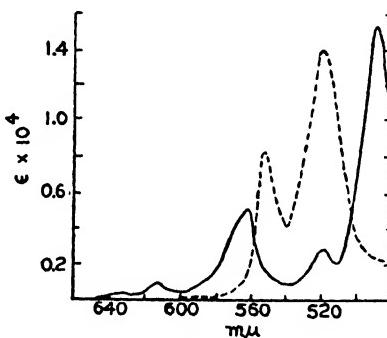


FIG. 14

tion is of little value, not only because it is not true for other classes of porphyrins, e.g., the methine-substituted porphines and for the imidoporphines (figure 15), but also because closer examination of the copper chlorine spectra often reveals within the complexity a second band with as great an absorption coefficient as the weaker of the two in the corresponding copper porphine.

Magnesium chelates of closely related porphines and chlorines show a relationship (figure 16) similar to the above.

The spectra for chlorophylls a and b, which were long a subject of controversy, now appear to be a matter of general agreement (43) (see figure 17). Most conspicuous is the extraordinarily high absorption coefficient for chlorophyll a in the red, being *ca.* 9.1×10^4 at its maximum, whereas most chlorines or phor-

bines, or their metal chelates, do not exceed two-thirds this value. Ultraviolet absorption spectra in various solvents are also available (13, 30). Some (4, 22) have believed that the position of the absorption maximum of chlorophyll a was not always a function of the index of refraction of the solvent (Kundt's rule). Mackinney (22) gave examples of additional failures for chlorophyll b in acetone ($N_D = 1.35886$) and dichloroethane ($N_D = 1.45026$) which have identical positions (and the importance of apparent deviations in visual instruments caused by skewness was emphasized). Egle (9), however, disputed Mackinney's findings as the result of investigations at different concentrations of

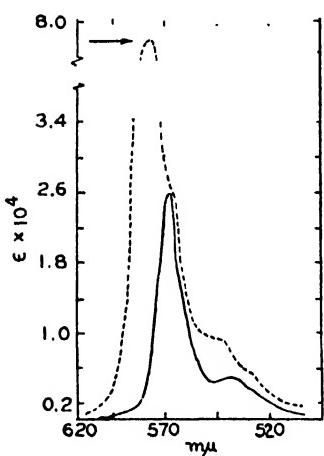


FIG. 15

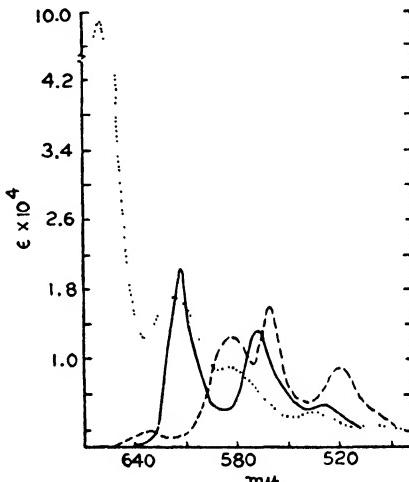


FIG. 16

FIG. 15. Absorption spectra of copper chelates of imidoporphines (from Pruckner and Stern (30)). —, copper salt of monoimidoetioporphine; - - -, copper salt of tetramethyl ester of β,δ -diimidocoprotoporphine II.

FIG. 16. Absorption spectra of chelates of corresponding porphines and phorbines (from Stern and Wenderlein (39)). —, magnesium salt of dimethyl ester of pheophorphine a*; - - -, dimethyl ester of pheophorphine a*; . . ., methylchlorophyllide a (magnesium salt of dimethyl ester of pheophorbine a).

chlorophylls a and b in different solvents (including the above) and attributed Mackinney's results to pheophytin formation. It is of interest to note that the data of Zscheile and Comar (43) on absorption spectra are not in agreement with Egle's, nor does the work (43) on the fluorescence of the chlorophylls (figure 18) show any relation between the wave length of the primary fluorescence and the refractive index of the solvent. While the earlier work of Stern *et al.* included spectra of a variety of examples of chlorophyll derivatives, a more recent specific study has been made by Stern and Pruckner (38). Additional spectra on some derivatives of bacteriochlorophyll have been given by Pruckner alone (27), as well as the dihydroxy derivatives of the chlorines (28), in which the hydrogen atoms in the 7- and 8-positions have been replaced by hydroxyl. In general, the bands

of the dihydroxy compounds are very similar in form and magnitude to those of the chlorines, but are shifted somewhat to the red. A further paper (29) is primarily concerned with the relation of structure to spectra. The results, e.g., of Calvin, Ball, and Aronoff's (5) interpretation of Rothemund's tetraphenylporphine

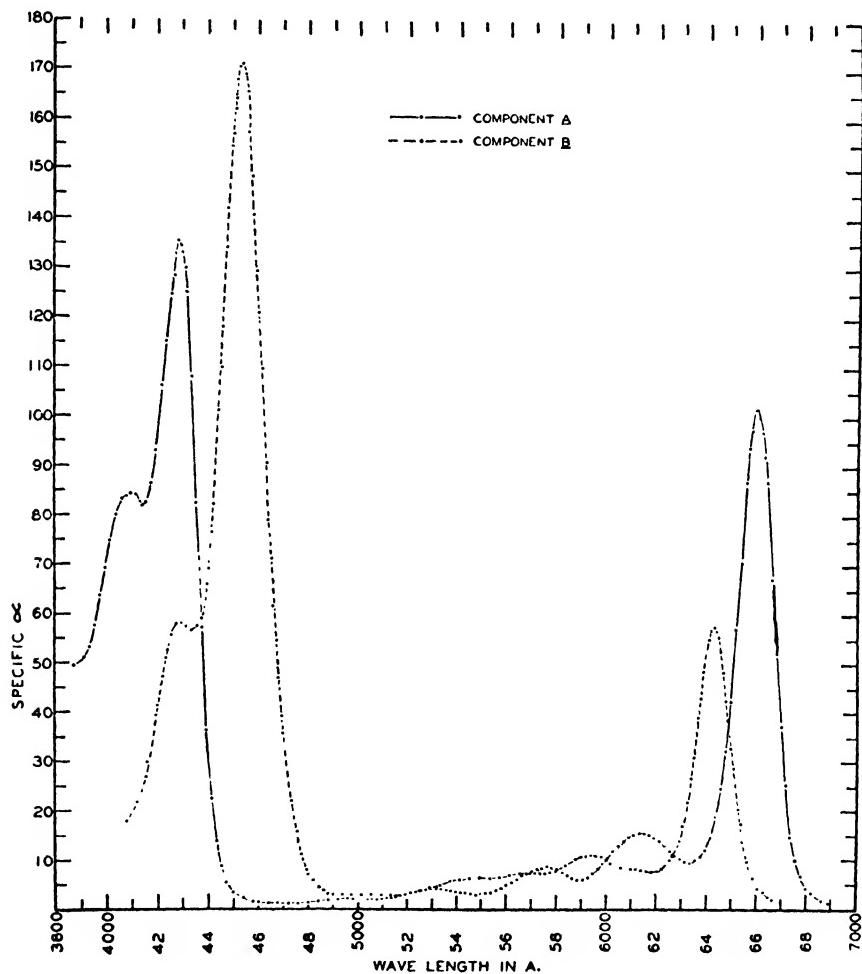


FIG. 17. Absorption spectra of chlorophylls a and b in ether (from Zscheile and Comar (43))

"isomers" as being due to the porphine and corresponding chlorine, are here also suggested. Rothemund remarks, in addition, that by comparison with the diimidoporphines, the chlorines are more "symmetrical" than the porphines, and that for this reason their general absorption is shifted toward the red. This point of view presumably stems from the "interference" in the resonance of the inner ring by coupling with the β -carbons in the pyrrole rings of porphines, a "disturb-

ance" which occurs to a lesser extent in the chlorines (*viz.* XIII and XIV). Nevertheless, a more generally accepted qualitative explanation of the shift of the primary absorption band in conjugated compounds is associated with an increased resonance or length of conjugation (see Lewis and Calvin (19)). Although the primary bands in the near ultraviolet of the chlorines and porphines are not significantly different in height or position, one interesting example is again found in tetraphenylchlorine, whose absorption coefficient in the ultraviolet is only half that of the corresponding porphine⁷. It is, however, still un-

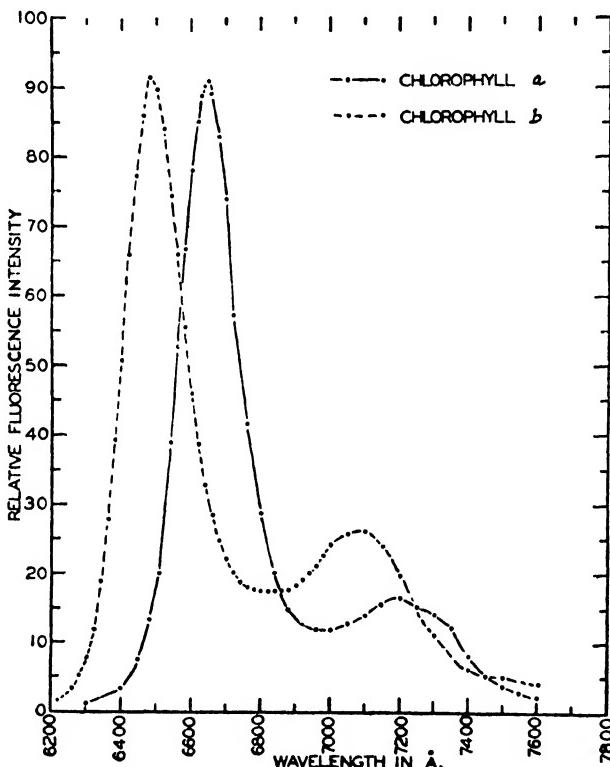


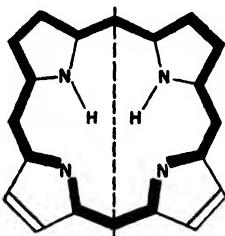
FIG. 18. Fluorescence spectra of chlorophylls a and b (from Zscheile and Harris (44))

explained as to why the addition of hydrogens to the β -positions in the pyrroles, a phenomenon which decreases the permissible resonance, should result in the formation of prominent bands in the red or infrared, aside from the improbability that the excited state is actually a dissociation (proton ejection), which would be easier with chlorines than with the nuclear hydrogens of porphines.

Three analyses of the spectra of porphyrins have appeared. An earlier and more elaborate scheme (15) gives a scheme of fundamentals for deuteroporphine (figure 19). Vibration frequencies of 1525 and 1145 cm^{-1} , ascribed to the $-\text{C}=\text{C}-$

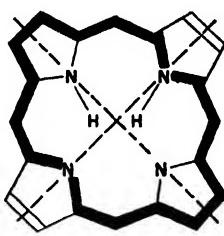
⁷ G. Dorough: Thesis, University of California, 1946.

conjugation, are made the basis of the term system. Vibrational states within the first electronic level are indicated, and the second electronic level, at 23,000 cm.⁻¹, is only inferred. The first main band in the red is ascribed to a vibrational band in the lowest level of the first electronic state, and subsequent bands to succeeding higher vibrational levels. The main band in the near ultraviolet presumably is another electronic transition. An almost identical scheme, of a more general character, has been suggested by Rabinowitch (31), who proposes, in addition, that the large red band in chlorines be ascribed to a new electronic



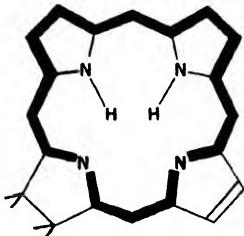
XIIIa

(symmetrical)



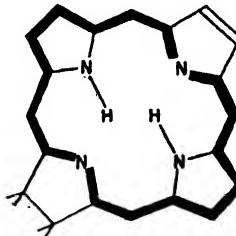
XIIIb

(symmetrical)

Some paths of π -electrons in porphines

XIVa

(unsymmetrical)



XIVb

(unsymmetrical)

Some paths of π -electrons in chlorines

transition of lower energy (figure 20a), with still a fourth, of even lower energy, for the tetrahydroporphines (bacteriochlorines) (figure 20b).

Very recently Simpson (32) has given a simplified LCAO calculation of the "center of gravity" of the bands of a porphine. In Simpson's model porphine is depicted as oscillating between the two tautomers XI and XII. Contributions of other forms are not considered but the system is "calibrated" by reference to the "center of gravity" of benzene. On the basis of a 24-electron system, calculations would indicate a center of gravity for the bands in the near infrared. Such absorption does not occur. On the basis of an 18-electron system in which the pair of double bonds not involved in the conjugation is neglected, and considering the conjugated system to be a circle, a center of gravity of 615 m μ

for the absorption bands is found. The ability to obtain a more correct result by neglect of the two nonconjugated double bonds is indeed interpreted as an indication of a partial lack of complete aromaticity. The argument is adduced that the reduction of a porphine to a chlorine does not change the position of the bands, and, indeed, by virtue of its asymmetry, diminishes degeneracy and

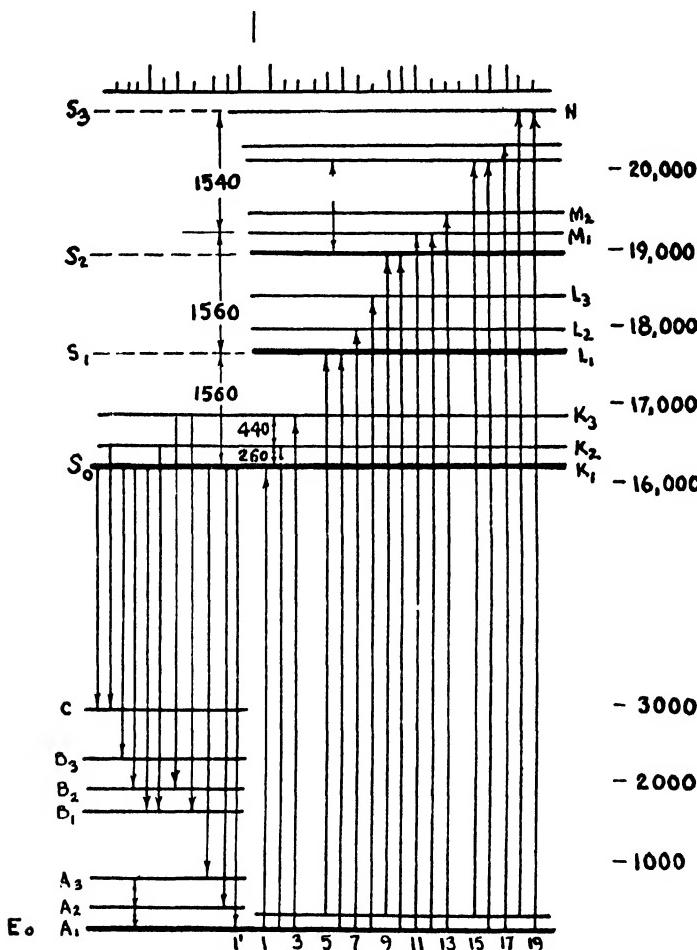


FIG. 19. Term system for deuteroporphine (from Hellström (15))

results in an increased absorption in the band of lowest frequency. This reasoning does not, however, explain why the addition of two more hydrogens as in bacteriochlorine, giving increased symmetry, should result in a new band, further in the infrared, also of very great intensity. This disappearance of bands in this acid spectrum is explained as a tendency of tautomerism to favor the tautomer in which the charges are at the greatest distance. A "free-electron gas"

approach, in calculation similar to Simpson's, has been suggested by H. Kuhn (17), but results of calculations and arguments are not yet available. These approaches show great promise in interpretation of porphyrin spectra.

Relatively little attention has been given to the infrared spectra of the porphines, primarily because of the difficulties encountered with the interpretation

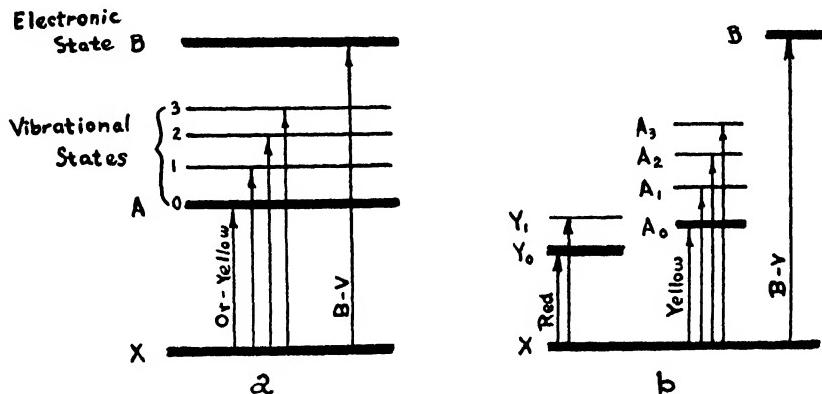


FIG. 20. Term system of (a) a porphine and (b) a chlorine (from Rabinowitch (31))

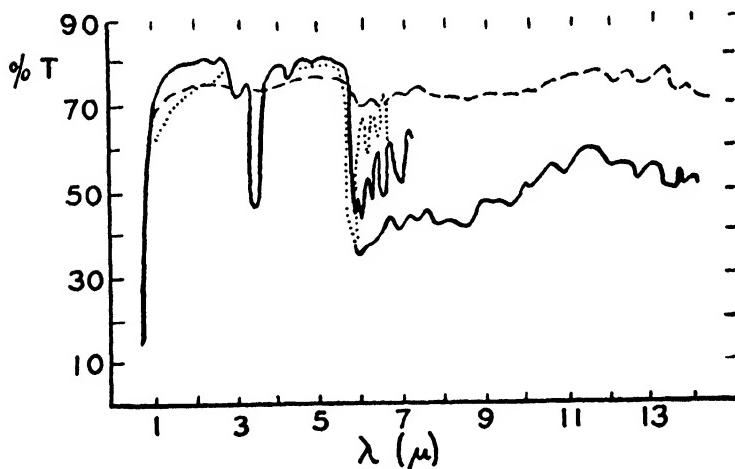


FIG. 21. Infrared spectra of chlorophyll and derivatives (from Stair and Coblenz (33)).
—, chlorophyll; . . ., pheophytin; - - -, ethyl chlorophyllide.

of such complex molecules. Two works on infrared spectra have appeared. Vestling and Downing (42) used this technique in an attempt to determine the degree of N—H—N bonding in porphines. As is well known, the infrared OH band of phenols disappears in chelates as of salicylaldehyde. It was of interest that these infrared studies showed a band not only in the dipyrromethenes, but also in the porphines at 3μ , where one would expect such a band from —NH. This

investigation did not rule out the possibility of N—H—N bonding, but neither did it substantiate it. A broader examination of the spectra was given earlier by Stair and Coblenz (33), in which spectra were presented for chlorophyll, pheophytin, copper pheophytin, ethyl chlorophyllide, phytol, "carotene," and xanthophyll in the region from 1 to 15 μ (figures 21 and 22). Two difficulties appeared prominent in this work. First, there was the complete disappearance of structure in ethyl chlorophyllide, including the band near 3 μ . Since this band is characteristic of compounds with —NH, or —OH, and apparently of the metal porphines (at least that of copper), there seems to be little reason to expect its disappearance. Indeed, on a logical deduction, from the pronounced appearance of this band in phytol (which is, of course, still present in pheophytin and its copper complex but not in ethyl chlorophyllide) one might have presumed that this

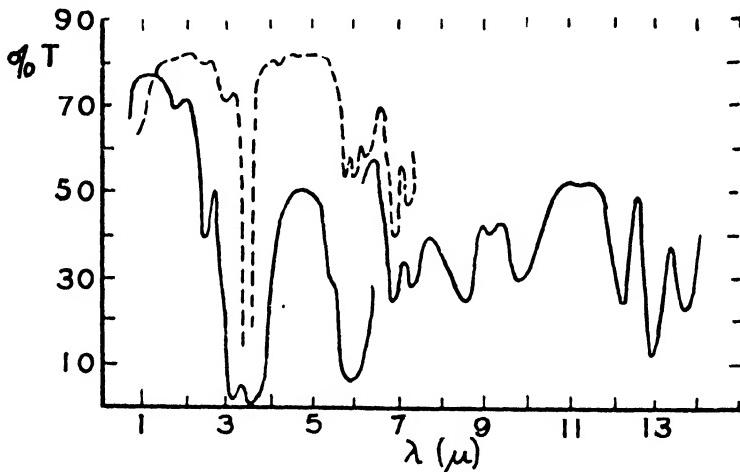


FIG. 22. Infrared absorption spectra of phytol and carotene mixture (from Stair and Coblenz (33)). —, phytol; ---, carotene (plus sterols?).

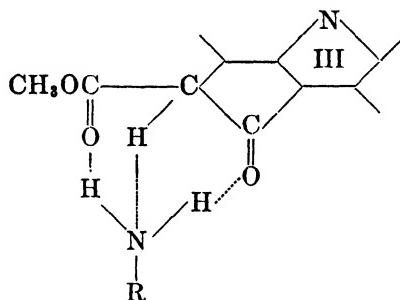
absorption band in chlorophyll was due solely to the presence of phytol. Another singularity was the presence of this same band in the hydrocarbon carotene. Although the material used was designated as crystalline, the known difficulty of separating sterols from carotenoids may account for this, in part.

FLUORESCENCE

The fluorescence spectra of chlorophylls a and b have been measured (44). Chlorophyll a in diethyl ether has a primary maximum at 665 m μ and a secondary at 720 m μ . Chlorophyll b has a similar structure, though shifted to the blue, with the corresponding maxima at 649 and 709 m μ . Variations, measured for the a component, are found in a variety of different solvents, the lowest being that for diethyl ether (664.5 m μ) and the highest for 2-ethyl-1-hexanol (676.5 m μ). The fluorescence is also temperature-dependent, the primary maximum being shifted to the red and increased in magnitude with decreasing temperature

(669.0 at -62°C . to 666.7 at 28°C .). No anti-Stokes fluorescence was found. The spectrum, as was already well known for the overall emission, was found to be independent of the wave length of the exciting source.

Livingston, Watson, and McArdle (20) have shown the necessity for the presence of polar solvent (0.01 per cent or more of the total solution) in order that chlorophyll should fluoresce in its normal yield. Fluorescence is almost nonexistent in the pure dry hydrocarbon. They explain their results by suggesting that the chlorophyll and the polar solvent form an addition compound (possibly via hydrogen bonding), the last being a requirement for fluorescence. Only those compounds which can form hydrogen bonds (with few exceptions, an outstanding one being ethyl ether) permit the fluorescence. The fluorescent entity is depicted as:



It would be interesting to know whether these same requirements for fluorescence hold for porphines and chlorines without the isocyclic ring and electro-negative substituent such as oxygen. Furthermore, unless the yield of the phosphorescence (or other long-lived state) is measured, we do not know whether or not such an entity is required for activation to the excited state. In other words, the possibility exists (until experimentation shows otherwise) that the function of these substances may be to diminish the yield of the long-lived state and that fluorescence may not be an indication of the ability of chlorophyll to react photochemically.

Hagene (12) has discussed briefly some of the visible changes of necrobiosis in chloroplasts. Two optical changes have been followed: the cessation of fluorescence and the displacement of the maximum. If chloroplasts are killed, e.g., by being placed in water at 50°C ., the fluorescence is gone after only 3 min., while the shift in the red band of chlorophyll (681 to $673\text{--}671\text{ m}\mu$) does not occur until 160 min. later. This obviously indicates that subtle changes, not visible in the absorption spectrum, occur rapidly, inactivating the assimilatory system.

Porphyrin-gelatin phosphors have been reported by both Bandow and Klaus (3) and Klaus (16). Unfortunately, the only portion of work reported by the first authors is concerned with the fluorescence, rather than the phosphorescence, properties of porphyrins in the solid state, although the existence of phosphorescence is mentioned. Vannotti indeed makes the highly interesting statement (41) that a phosphorescence with a duration of 0.01–1.0 sec. is present, quoting from

Klaus (whose thesis has been unavailable to the writer). Of particular and inexplicable interest is the statement by Vannotti that only wave lengths of the region 580–640 m μ can excite phosphorescence. The assumption has been made that no difficulty is found in the transition from the second electronic state (the large band in the ultraviolet) to the first. This is substantiated by the fact that all porphines have the same characteristic fluorescence spectra regardless of the wave length of the absorbed light. A phosphorescence of chlorophyll has long been sought as an aid in explaining the kinetics of photosynthesis. This has recently been found by Calvin and Dorough (6, 7) who, following the theory of Lewis and Kasha (18), identify the phosphorescence with a forbidden transition from the triplet to the singlet state. The lifetime of chlorophyll phosphorescence was then estimated at 0.2 sec. (6). In more recent work with purified pigments (7) it was found that the reported phosphorescence occurs only with chlorophyll b, with a lifetime of 0.03 sec. The existence of a long-lived state for chlorophyll a is thus still open to question. Furthermore, the diminution in the lifetime of the phosphorescence upon the purification of chlorophyll suggests that in the natural state, where the high concentrations of chlorophyll (ca. 0.1 M) permit energetic coupling of adjacent molecules, the above value may not be quantitative for chlorophyll b or even qualitative for chlorophyll a.

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RECENT INVESTIGATIONS ON ERGOT ALKALOIDS¹

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As a result of the combined efforts of chemists and biologists, numerous fungi have, in the last few years, been brought into the forefront of scientific interest. From these low forms of life, extremely valuable therapeutic agents have been derived. These are the so-called "antibiotics," which are among the most powerful weapons available in the fight against infectious diseases. That fungi can provide useful remedies is, however, no new discovery. The fungus *Claviceps purpurea*, which produces the ergots seen in the ears of infected rye, has been employed on a purely empirical basis in popular medicine for several hundred years and has claimed the interest of numerous research workers for many decades.

This review will not deal in detail with the interesting history of ergot, an excellent account of which is given in George Barger's monograph *Ergot and Ergotism*, published in 1931, but will start with the most recent stage in the development of ergot research, that which began somewhere around the year 1920 with the isolation and preparation in a pure state of the first homogeneous ergot alkaloid, ergotamine. The idea that the active principles of ergot are alkaloids only began to find general acceptance about twenty-five years ago. Since then, the ergot alkaloids and the derivatives prepared from them synthetically have become valuable and, in some cases, indispensable remedies in the most varied fields of medicine.

The natural alkaloids of ergot which have so far been isolated are shown in table 1. Their classification into three groups—the ergotamine group, the ergo-toxine group, and the ergobasine (ergonovine) group—is based upon differences in their chemical structure. As this table shows, the ergot alkaloids occur in pairs. The two alkaloids of a pair are stereoisomers and each readily undergoes rearrangement to the other. This isomerism is due to the isomerism between lysergic and isolysergic acids, the parent compounds from which all the alkaloids of ergot are derived. Whether existing independently or forming part of the alkaloid molecule, lysergic acid readily undergoes rearrangement to the isomeric isolysergic acid and *vice versa*. The natural levorotatory ergot alkaloids are derived from lysergic acid, whereas the isomeric dextrorotatory members of the pairs are derived from isolysergic acid. This isomerism is bound up with a number of interesting problems which will be discussed later. It is important to note that the natural levorotatory alkaloids have a powerful pharmacological action, whereas the corresponding dextrorotatory compounds possess only a fraction of the activity of their levorotatory isomers.

¹ Based on a lecture delivered before the Organic Colloquium at Harvard University on May 9, 1950.

Before considering the structure of the ergot alkaloids, attention should be directed to a few points in connection with the individual alkaloids listed in table 1. The first five pairs of alkaloids are presented in the chronological order of their discovery. The first is the alkaloid pair ergotamine—ergotaminine. Ergotamine (14) was isolated in crystalline form and subjected to chemical analysis as long ago as 1918. Not long afterwards, the observation was made that it could readily be converted into the strongly dextrorotatory but pharmacologically less active ergotaminine.

TABLE I
The natural alkaloids of ergot and their dextrorotatory isomers

NAME	FORMULA	[α] _D ²⁰ IN CHCl ₃	DISCOVERER
1. Ergotamine group:			
Ergotamine	C ₃₃ H ₃₅ O ₆ N ₅	-155°	Stoll (1918)
Ergotaminine		+385°	
2. Ergotoxine group:			
Ergocristine	C ₃₆ H ₃₉ O ₆ N ₅	-183°	Stoll and Burekhardt (1937)
Ergocristinine		+366°	
Ergokryptine	C ₃₂ H ₄₁ O ₆ N ₅	-187°	Stoll and Hofmann (1943)
Ergokryptinine		+408°	
Ergocornine	C ₃₁ H ₃₉ O ₆ N ₅	-188°	Stoll and Hofmann (1943)
Ergocorninine		+409°	
3. Ergobasine group:			
Ergobasine	C ₁₉ H ₂₃ O ₂ N ₃	-44°	Dudley and Moir Kharasch and Legault
Ergobasinine		+414°	Stoll and Burekhardt Thompson (1935)

Preliminary experiments on the pharmacological properties of pure ergotamine carried out by Stoll, together with the investigations of Spiro (13) and the somewhat later and more detailed studies of Rothlin, showed that ergotamine in very small doses possesses the entire action of a good ergot preparation, a fact which was confirmed by the first clinical trials. It was found that in obstetrics and gynecology, the only field of application of ergot at that time, ergotamine could be employed with complete satisfaction in all the indications. It was thus clear that the specific active principles of ergot must be alkaloids, a fact which was of decisive importance for the further development of the chemistry and pharmacology of ergot. Nevertheless, until about 1925, and in some places still

later, the view was prevalent that the ergot alkaloids had given disappointing results when used clinically and that the therapeutic significance of ergot could not, therefore, be due to its alkaloid content. The very numerous pharmacological and clinical studies carried out with ergotamine accomplished valuable pioneer work, yet the view which is generally accepted today, that the specific active principles of ergot are alkaloids, only really took root after the discovery of ergobasine (ergometrine, ergonovine) in the middle of the 1930's.

The second pair of alkaloids in table 1, ergosine and its isomer ergosinine, was isolated by Smith and Timmis (12) in 1936, but neither alkaloid has yet been introduced into medicine.

Although there are a number of peculiar features connected with the discovery and chemical investigation of the three pairs of alkaloids comprising the ergotoxine group—ergocristine—ergocristinine, ergokryptine—ergokryptinine, and ergocornine—ergocorninine—it is only possible in this review to give a brief account of the research. In 1906, an apparently homogeneous but amorphous alkaloid preparation was isolated from ergot by Barger and Carr (1) in England and simultaneously by the Swiss pharmacist Kraft (11). The latter investigator designated the product "hydroergotinine," but the name *ergotoxine* is the one which has become universally accepted in the literature. As the result of various chemical and pharmacological investigations and considerations, it was shown that, although ergotoxine had in the meantime been obtained in a crystalline form, it was nevertheless not a homogeneous substance but a mixture of three isomorphous ergot alkaloids. One of these, ergocristine (16), had already been isolated in 1937, while the other two were previously unknown and were named ergokryptine and ergocornine (19).

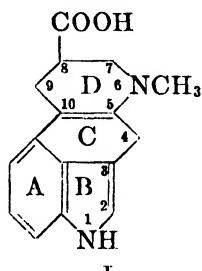
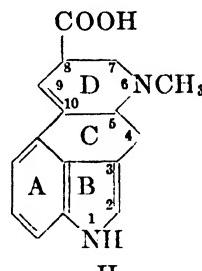
All the alkaloids of ergot, including ergobasine, contain either lysergic acid or isolysergic acid as the principal and characteristic constituent of the molecule. The alkaloids of the ergotamine and ergotoxine groups are polypeptides, the lysergic or isolysergic acid being joined to other amino acids. They thus occupy a special place among the vegetable alkaloids.

The last pair of alkaloids shown in table 1, ergobasine—ergobasinine, has a simpler structure, lysergic acid or isolysergic acid being combined merely with an aminoalcohol. Shortly after Jacobs (6) had established the composition of ergobasine—which is known in England as ergometrine and in America as ergonovine—its partial synthesis, the first to be achieved in the field of ergot chemistry, was accomplished by Stoll and coworkers.

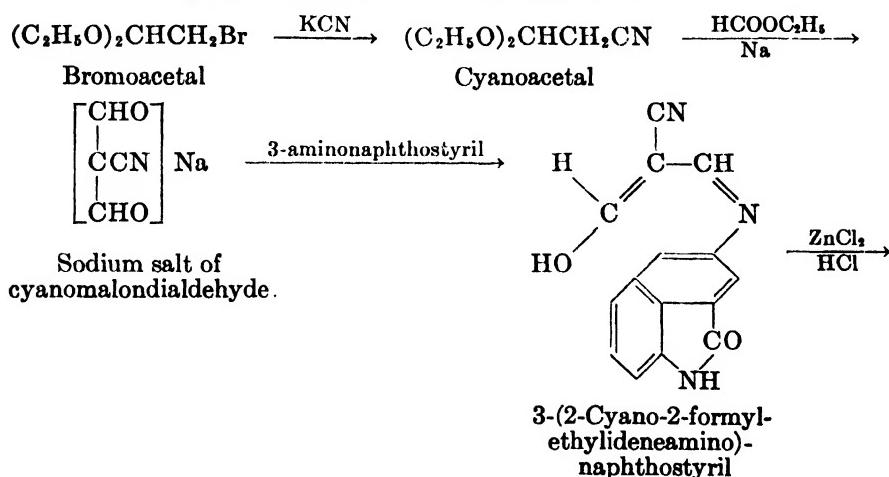
The investigations on the constitution of the ergot alkaloids proceeded along two independent paths, being concerned, on the one hand, with the structure of the lysergic acid portion of the molecule and, on the other, with that of the basic side chain connected with it. While all the details regarding the structure of the lysergic acid portion have now been established with certainty, the constitution of the peptide portion is still being ardently investigated. A closely connected question is that of the linkage between the peptide portion and lysergic acid, regarding which no very definite information is yet available.

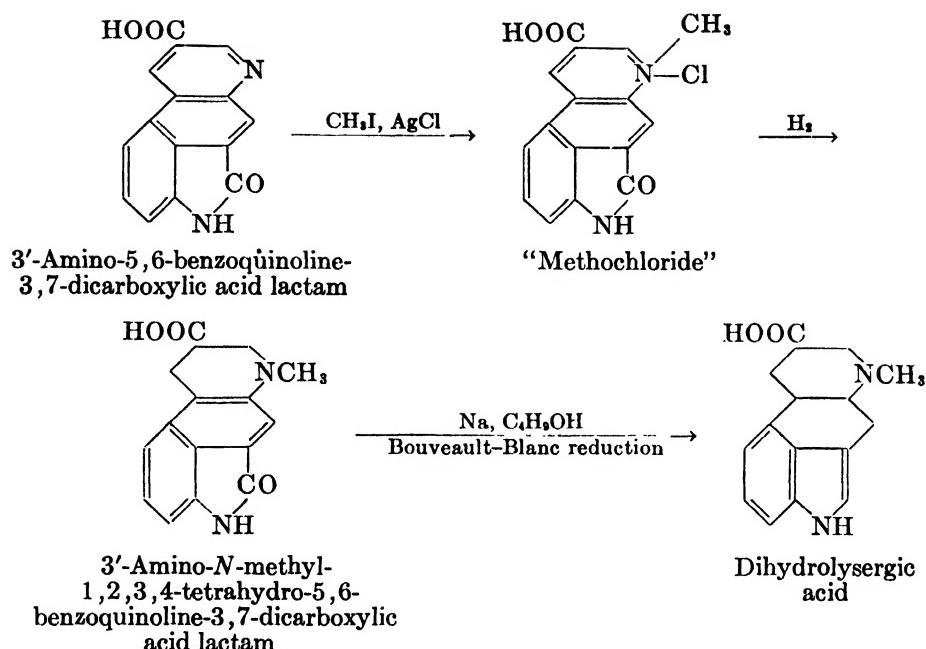
Fundamental knowledge regarding the structures of lysergic and isolysergic acids and of the individual components of the peptide portion is due to the in-

vestigations carried out by Jacobs and Craig at the Rockefeller Institute in New York City. Thus, from cleavage products obtained by the action of energetic reagents, Jacobs (3, 9) was able, as far back as 1938, to deduce formulas for lysergic acid and isolysergic acid which were in agreement with their reactions and with structural considerations.

I
Lysergic acid (Jacobs)II
Isolysergic acid

In these formulas the following groups may be clearly recognized: an indole system (rings A and B), a naphthalene system (rings A and C), and an *N*-methylquinoline system (rings C and D). The difference between lysergic acid and isolysergic acid was attributed by Jacobs to a difference in the position of the double bond in ring D. This double bond is readily hydrogenated, giving rise to corresponding dihydro acids. Since, according to the above formulation, the dihydro acids exhibit asymmetric carbon atoms at positions 5, 8, and 10, it was to be anticipated that saturation of the double bond with hydrogen would lead to complicated racemic mixtures. This, in fact, proved to be the case. Bearing in mind these complications, Uhle and Jacobs (28) in 1945 carried out the total synthesis of a mixture of racemic dihydrolysergic acids and thus proved the correctness of the *skeleton* in their formula for lysergic acid. The following scheme illustrates the highly original synthesis employed by them:





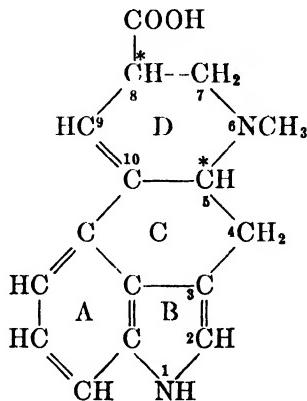
The starting point in this synthesis was bromoacetal, which was converted by means of potassium cyanide into cyanoacetal. This was subsequently treated with ethyl formate and sodium to give the sodium salt of cyanomalondialdehyde, which Uhle and Jacobs then reacted with 3-aminonaphthostyryl. In this way they obtained 3-(2-cyano-2-formylethylideneamino)naphthostyryl. On treatment with zinc chloride and hydrochloric acid, this compound yielded 3'-amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam, which was converted into the corresponding methochloride by means of methyl iodide and silver chloride. By catalytic hydrogenation of this methochloride, Uhle and Jacobs were able to obtain 3'-amino-*N*-methyl-1,2,3,4-tetrahydro-5,6-benzoquinoline-3,7-dicarboxylic acid lactam which, on treatment with sodium in boiling butanol, gave a very small yield of racemic dihydrolysergic acid.

The totally synthetic preparation obtained in this way proved to be identical with the product prepared by catalytic hydrogenation of the racemic lysergic acid of natural origin. In both cases the product obtained was a mixture of racemates.

After the ring system of lysergic acid and the nature and position of the substituents (carboxyl, methyl) had been established by Uhle and Jacobs by the total synthesis of dihydrolysergic acid, there remained two further questions of importance regarding the fine structure of lysergic acid still to be settled: (1) the position of the readily reducible double bond in ring D and (2) the mechanism of the reaction by which lysergic acid isomerizes to isolysergic acid and *vice versa*.

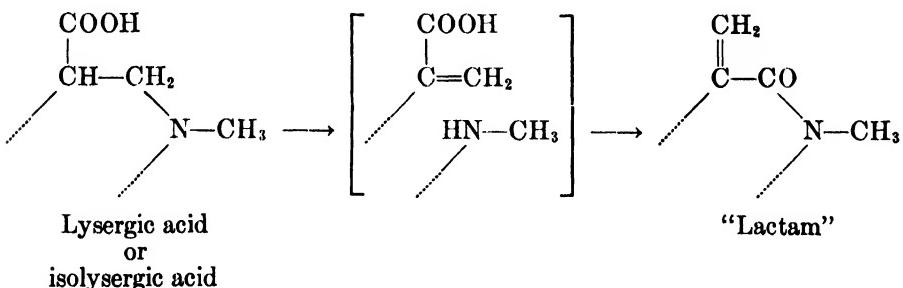
The hypothesis advanced by Jacobs that the double bond migrates from the 5,10-position to the 9,10-position during the isomerization of lysergic acid to isolysergic acid did not provide a satisfactory explanation for the process.

The results of recent investigations by Stoll and coworkers (22) furnished proof that the double bond is in the 9,10-position in both acids. Accordingly, lysergic acid and isolysergic acid have the following constitution:

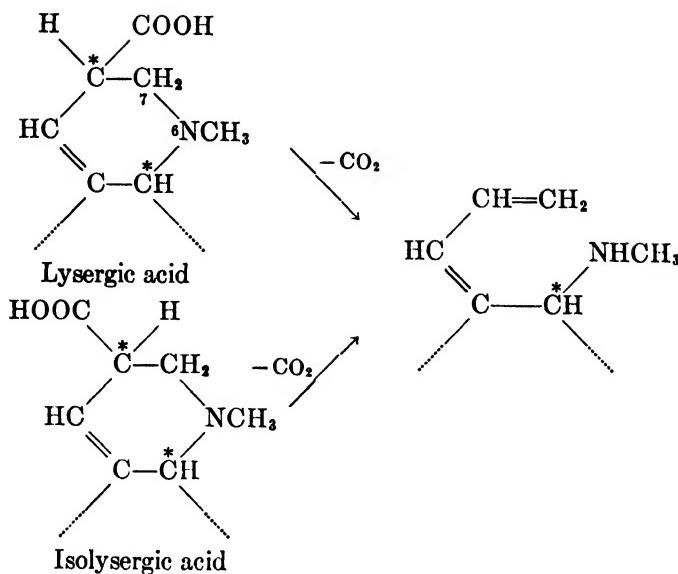


Lysergic acid; isolysergic acid

It would take too long to present in detail the experiments which have led to this conclusion. The main basis for the deductions was the finding that both lysergic acid and isolysergic acid react like β -aminocarboxylic acids on heating with acetic anhydride, i.e., with opening of ring D, and that subsequently lactam formation takes place between the secondary amino group and the carboxyl group:



In these degradation experiments it was found that both lysergic acid and isolysergic acid gave rise to the same lactam. The position of the readily reducible double bond must therefore be the same in both acids. This conclusion is also in agreement with the results of decarboxylation experiments on lysergic acid and isolysergic acid, both compounds yielding the same product, as shown in the following scheme:



During this decarboxylation (22) not only is the carboxyl group split off, but the linkage between nitrogen atom 6 and carbon atom 7 is also broken. The

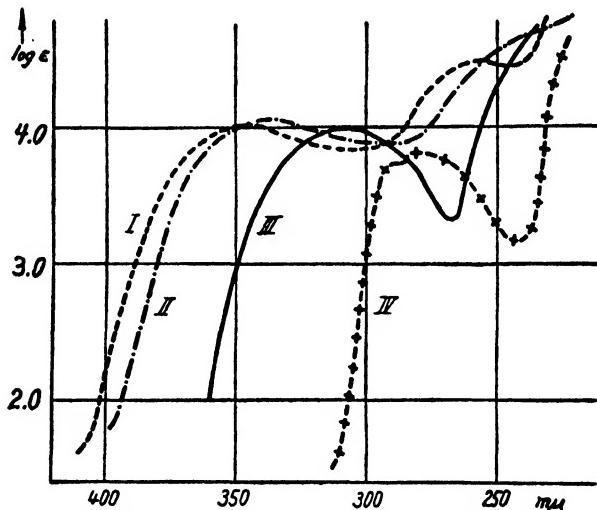
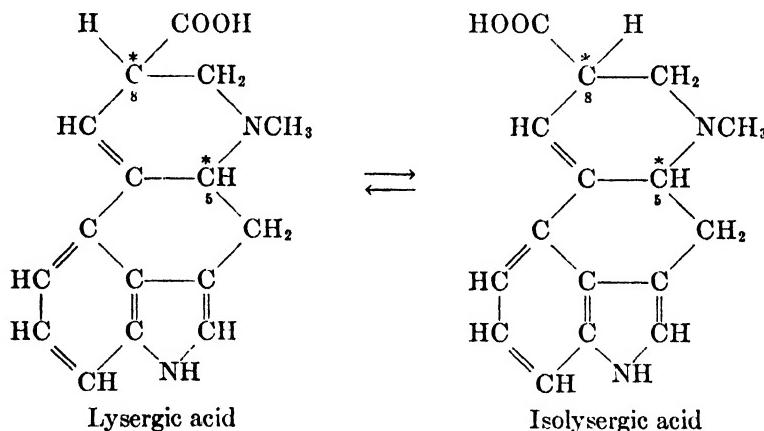


FIG. 1. Ultraviolet absorption spectra. Curve I, lactam obtained from lysergic acid or isolysergic acid; curve II, product obtained by the decarboxylation of lysergic acid or isolysergic acid; curve III, lysergic acid or isolysergic acid; curve IV, dihydrolysergic acid.

ultraviolet absorption spectrum of the decarboxylated product indicates clearly that the newly formed double bond between C-7 and C-8 is conjugated with the double bond already present, which must therefore be between carbon atoms

9 and 10. The chromophore system of this decarboxylation product is identical with that of the lactam just discussed, a fact which was confirmed by the agreement between the absorption spectra of the two compounds (see figure 1).

On the assumption that a double bond is present between carbon atoms 9 and 10, lysergic acid must have two asymmetric centers, one at C-5 and the other at C-8. That both lysergic acid and isolysergic acid possess a second asymmetric center in addition to that at C-8 was proved by the fact that the lactam previously discussed is *optically active*, although the asymmetric center at C-8 is no longer present. These facts also indicate that lysergic acid and isolysergic acid have the same configuration at C-5 and, since the double bond in ring D is situated in the same position, $\Delta^{9,10}$, in both acids, the only difference between them must be in the spatial arrangement of the substituents at C-8. Available evidence indicates that in lysergic acid the carboxyl group is nearer nitrogen atom 6 than it is in isolysergic acid. The following formulas illustrate these relationships:



As already mentioned, natural D-lysergic acid² and natural D-isolysergic acid have an identical configuration at C-5 and differ only in their configuration at C-8. Theoretically, however, either the D- or the L-configuration may be present at each of the two asymmetric carbon atoms 5 and 8. This may be represented schematically as follows:



By combining these four possibilities, the following four optically active isomers are obtained:

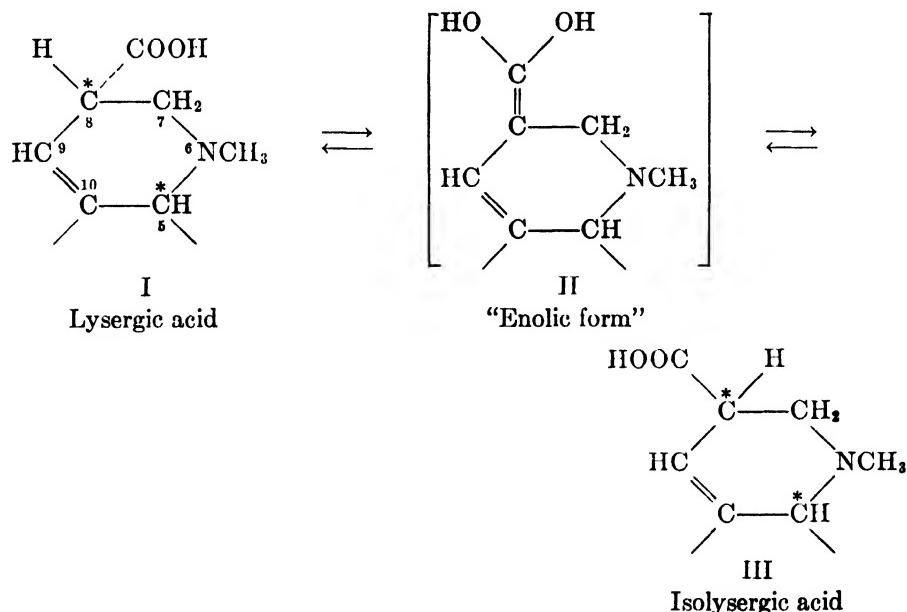


³ The small capitals D and L used in this publication refer to the configurations of the compounds in question. They give no information regarding the direction of the optical rotations, natural lysergic acid having been designated as D-lysergic acid.

I and III are optical antipodes and so are II and IV. On the other hand, I and II are diastereoisomers and the same relationship applies to III and IV. As can be gathered from this schematic representation, I and II and also III and IV agree in the configuration at C-5 and differ only in the configuration at C-8. Thus, either I and III are the two optical antipodes of lysergic acid while II and IV are the optical antipodes of isolysergic acid, or *vice versa*. Both possibilities must be taken into consideration, since the absolute configuration is not known either at C-5 or at C-8.

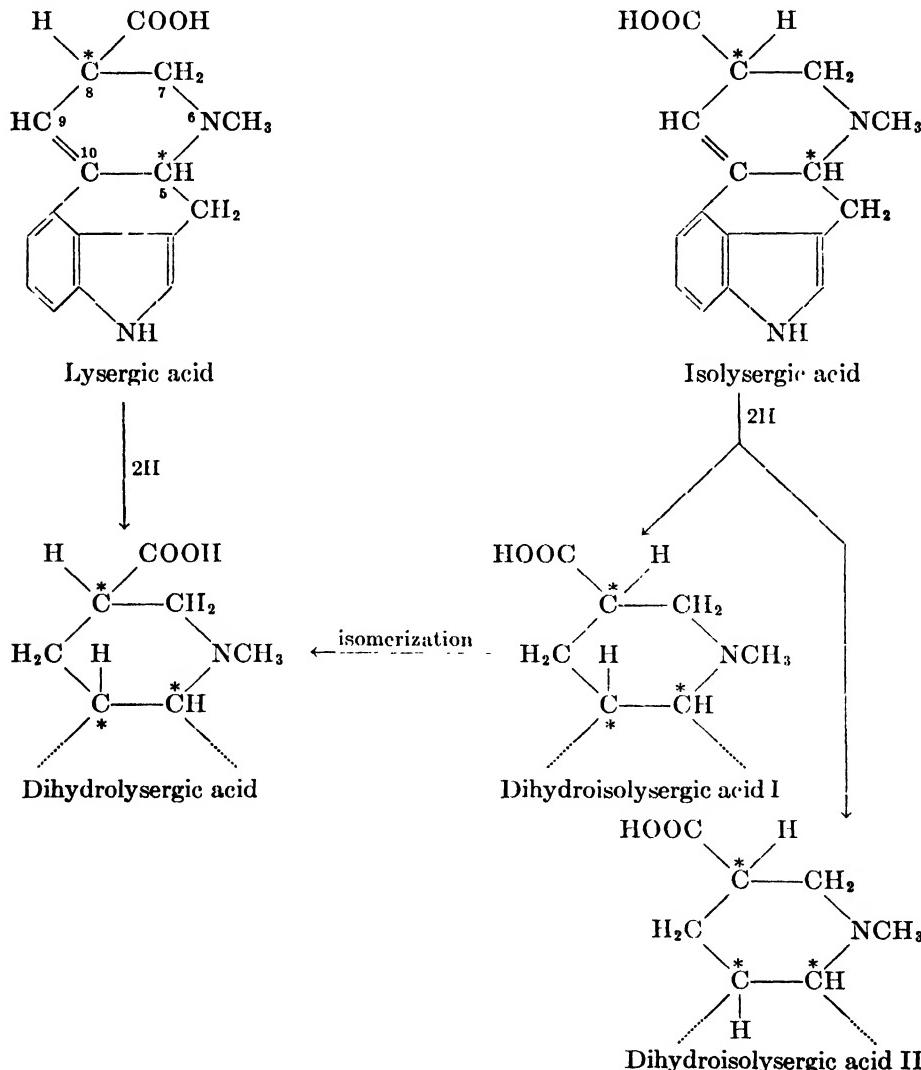
Practical experience with lysergic acid and isolysergic acid is in complete agreement with these theoretical considerations. Both natural D-lysergic acid and its optical antipode L-lysergic acid are known, as well as D-isolysergic acid and L-isolysergic acid. The two corresponding racemates have likewise been prepared.

These steric relationships having been elucidated, a simple explanation is available for the conversion of lysergic acid into isolysergic acid and *vice versa*. Enolization of the carboxyl group at position 8 leads to the intermediate formation of an acid enolate (II) which subsequently rearranges once more to the acid form, with the result that an alteration may take place in the configuration of the substituents at C-8.



These formulas also enable an explanation to be given for the observations regarding the catalytic hydrogenation of lysergic acid and isolysergic acid. With the saturation of the double bond in ring D, a new asymmetric center is produced at C-10 and both lysergic acid and isolysergic acid may therefore be expected *a priori* to yield two partial racemates. This in fact occurred, since hy-

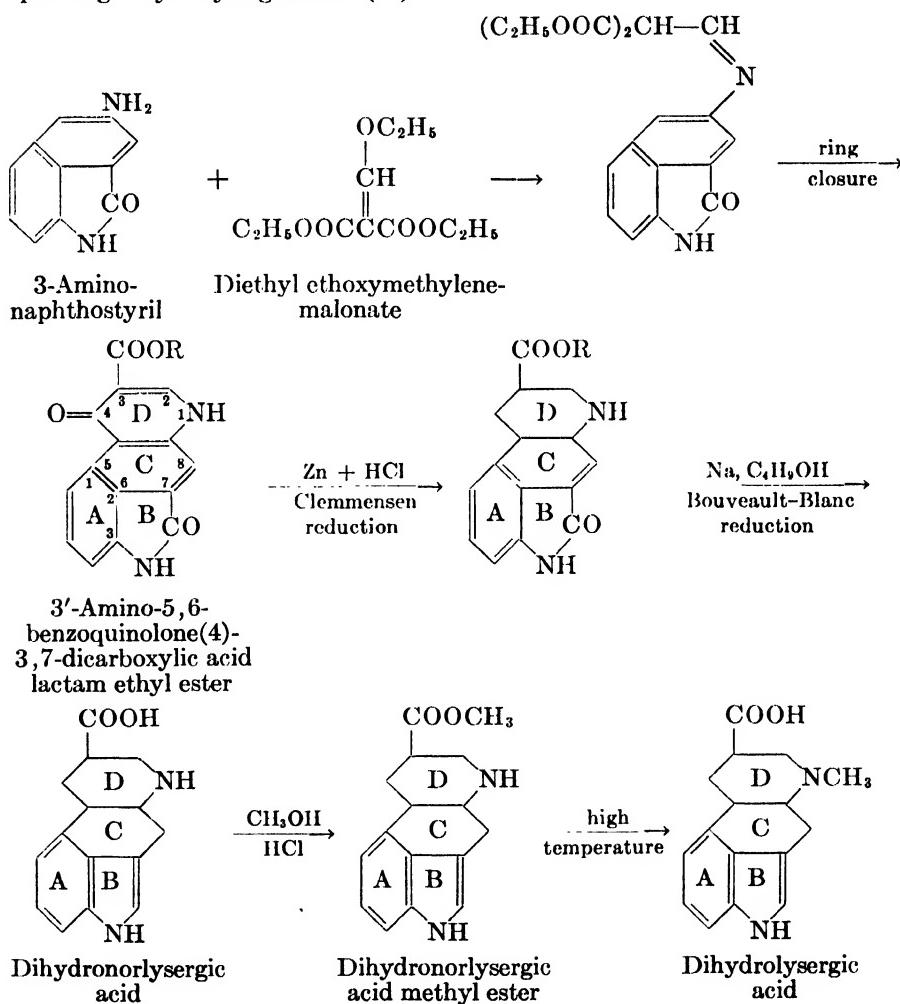
drogenation of isolysergic acid yielded two well-defined dihydroisolysergic acids, which were denoted by the Roman numerals I and II. Hydrogenation of lysergic acid, however, yielded only one dihydrolysergic acid. As may be seen from the following formulas, the isomerism between dihydroisolysergic acid I and dihydroisolysergic acid II is due to a difference in the spatial arrangement of the hydrogen atom at C-10. In the formulas depicted the orientations have been chosen arbitrarily.



As may be gathered from these formulas, the orientation of the hydrogen atom at C-10 in dihydrolysergic acid is the same as that in dihydroisolysergic acid I, the only difference between the two compounds being in the configuration at C-8.

The synthesis of dihydrolysergic acid perforse gives rise to an optically inactive mixture which presumably contains the racemates of the three dihydro acids mentioned above. For purposes of comparison, natural lysergic acid was converted *via* the hydrazide to the racemates of isolysergic acid and lysergic acid, which were then subjected to catalytic hydrogenation to yield racemic dihydrolysergic acid and the racemic dihydroisolysergic acids I and II.

The next stage in the investigations concerned a synthesis of dihydronorlysergic acids (24), in which the nitrogen atom at position 6 carries no methyl group, and subsequent methylation of this nitrogen atom to yield the corresponding dihydrolysergic acids (25).



The starting material for this synthesis was 3-aminonaphthostyryl, which was condensed with diethyl ethoxymethylenemalonate according to the directions

given by Gould and Jacobs (5). Ring closure of the intermediate product so obtained yielded 3'-amino-5,6-benzoquinolone(4)-3,7-dicarboxylic acid lactam ethyl ester, which had also been previously prepared by Jacobs. With the aid of the Clemmensen reduction, the carbonyl group in position 4 of this ester was reduced to a CH_2 group. The resulting compound was subjected to further reduction by the method of Bouveault-Blanc and, in this way, there was obtained a racemic mixture of the three acids: dihydronorlysergic acid, dihydro-norisolysergic acid I, and dihydronorisolysergic acid II. The dihydronorlysergic acid was esterified with methanol and anhydrous hydrogen chloride to give dihydronorlysergic acid methyl ester. With the aid of a new type of rearrangement, involving migration of the methyl group, a conversion of this methyl ester into dihydrolysergic acid was effected. This reaction was carried out by heating the dihydronorlysergic acid methyl ester to a high temperature, whereupon the ester methyl group migrated to nitrogen atom 6. This reaction has been studied further and has been extended to other compounds, of which hygrinic acid and guvacoline may be mentioned as examples. In a similar manner, the methyl ester of dihydronorisolysergic acid I may also be converted to dihydrolysergic acid I.

The problems connected with the optical activity of these compounds were studied next. Thus, the synthetic, racemic dihydrolysergic acid was resolved into its optical antipodes, in this way accomplishing the first synthesis of D-dihydrolysergic acid which is derived from natural D-lysergic acid. This acid forms the parent substance of the dihydroalkaloids, dihydroergotamine, dihydroergocristine, dihydroergocornine, and dihydroergokryptine, which have now assumed considerable therapeutic importance.

The resolution of the racemic dihydrolysergic acid was accomplished in the following manner: The racemate was first converted to the methyl ester, which was then transformed into the hydrazide by means of anhydrous hydrazine. The racemic dihydrolysergic acid hydrazide was treated with nitrous acid, yielding racemic dihydrolysergic acid azide, which was allowed to react with L-norephedrine. As expected, the D-dihydrolysergic acid L-norephedride and the L-dihydrolysergic acid L-norephedride so obtained possess different chemical and physical properties and could be separated from one another by chromatography. In this way, the synthesis of D-dihydrolysergic acid L-norephedride as well as that of D-dihydrolysergic acid itself, which was obtained on alkaline hydrolysis, was accomplished for the first time. Data regarding some properties of these compounds are summarized in table 2.

Research on the fine structure of the basic fragment of the ergot alkaloid molecule, the peptide residue, has proved much less fruitful than in the case of the lysergic acid portion. It is true that forty years ago Barger and Ewins (2) had already shown that thermal decomposition of ergotoxine preparations yields the amide of dimethylpyruvic acid, while about fifteen years ago, Jacobs and Craig (7) were able to isolate from the alkaline cleavage of ergotinine and ergotamine not only lysergic acid but also two amino acids. One of these was proline in both cases, whereas the other differed according to the alkaloid. These in-

vestigations marked the first steps in elucidating the constitution of the peptide portion in alkaloids of the ergotamine type and subsequently led to extensive knowledge regarding the various units from which the peptide portions are built up in all the known alkaloids of ergot. The following cleavage products, for

TABLE 2
Properties of synthetic dihydrolysergic acids and their L-norephedrides

SUBSTANCE	$[\alpha]_D^{20}$	MELTING POINT °C.
D-Dihydrolysergic acid L-norephedride.....	-114°	240-241
L-Dihydrolysergic acid L-norephedride.....	+107°	252-253
D-Dihydrolysergic acid	-120°	Above 300 (decomposition)
L-Dihydrolysergic acid	+120°	Above 300 (decomposition)

TABLE 3
Ergot alkaloids of the polypeptide type
Structural units of all these alkaloids: lysergic acid radical, ammonia, D-proline

	WITH PYRUVIC ACID: ERGOTAMINE GROUP		WITH DIMETHYLPYRUVIC ACID: ERGO-TOXINE GROUP	
	With lysergic acid	With isolysergic acid	With lysergic acid	With isolysergic acid
With L-phenylalanine.....	ergotamine \rightleftharpoons ergotaminine $C_{33}H_{55}O_6N_5$		ergocristine \rightleftharpoons ergocristinine $C_{35}H_{57}O_6N_5$	
With L-leucine.....	ergosine \rightleftharpoons ergosinine $C_{30}H_{57}O_6N_5$		ergokryptine \rightleftharpoons ergokryptinine $C_{32}H_{61}O_6N_5$	
With L-valine.....			ergocornine \rightleftharpoons ergocorninine $C_{31}H_{59}O_6N_5$	

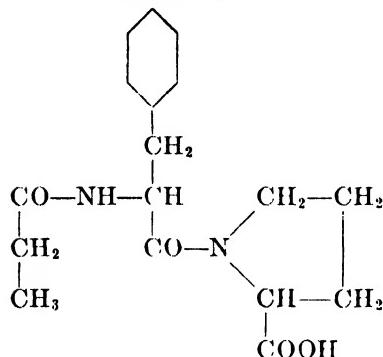
example, have been isolated from ergotamine:

Lysergic acid amide.....	$C_{19}H_{31}ON_3$
Pyruvic acid.....	$C_3H_4O_3$
L-Phenylalanine.....	$C_9H_{11}O_2N$
D-Proline.....	$C_6H_9O_2N$
	$-3H_2O \quad C_{33}H_{55}O_6N_5 \quad \text{Ergotamine}$

As far back as 1938, Jacobs and Craig (8) demonstrated that the keto acid is not present as such in the ergotamine molecule but is formed from a precursor, the constitution of which is still unknown. A few years later, Stoll isolated from ergotamine L-phenylalanyl-D-proline lactam, which was the first large fragment of the peptide portion of this alkaloid to be obtained. His most recent investigations (23), which have been carried out mainly with the more stable dihydroalkaloids, have enabled some insight to be obtained into the structure of the peptide portion. In fact, it has proven possible to split off the *peptide residue*

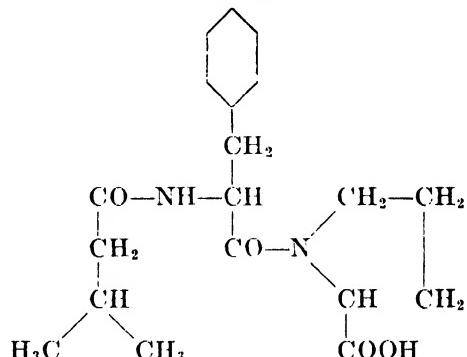
as a whole from practically all ergot alkaloids having a peptide structure, and the constitution of this peptide portion has been elucidated and its structure confirmed synthetically. Since, however, the peptide residue was split off by means of anhydrous hydrazine, the precursor of the keto acid was not obtained in its original form but as a reduced derivative. The products which were obtained from the dihydroalkaloids by cleavage with anhydrous hydrazine are shown in the following diagram:

From dihydroergotamine



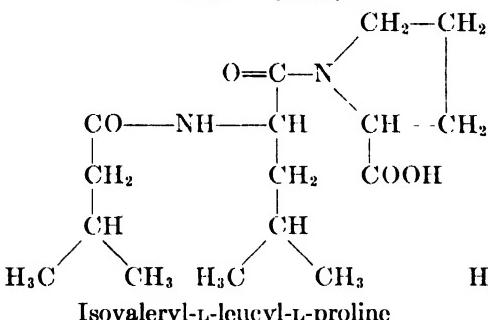
Propionyl-L-phenylalanyl-L-proline

From dihydroergocristine



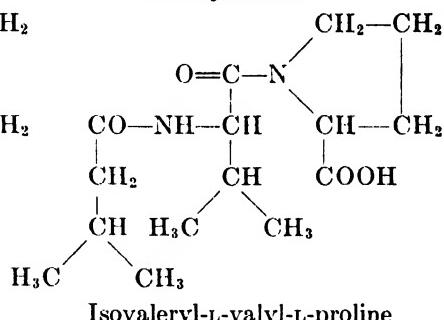
Isovaleryl-L-phenylalanyl-L-proline

From dihydroergokryptine



Isovaleryl-L-leucyl-L-proline

From ergocornine



Isovaleryl-L-valyl-L-proline

From this diagram it is very easy to see in which structural units the ergot alkaloids differ from one another. The lysergic acid portion of the molecule and the linkage between it and the peptide residue are the same in all the alkaloids. In the members of the ergotamine group the precursor of the keto acid, which is united directly with lysergic acid, possesses the carbon skeleton of propionic acid, whereas in the alkaloids of the ergotoxine group it is derived from isovaleric acid. This constitutes the only point of difference between ergotamine and ergocristine. In ergokryptine and ergosine, however, L-phenylalanine is replaced by L-leucine and in ergocornine by valine.

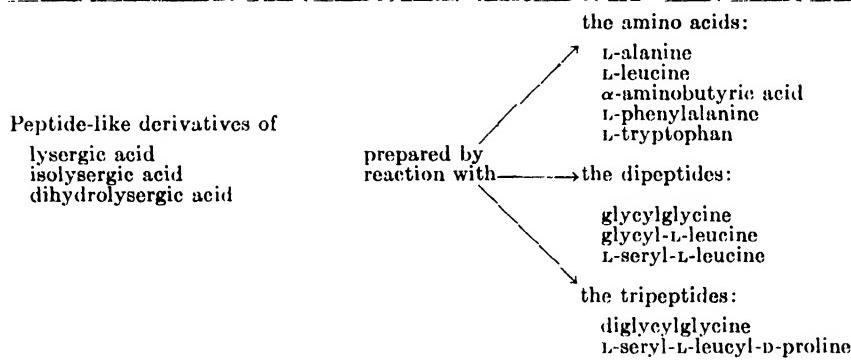
A summary of all the units from which the alkaloids of ergot of the polypeptide type are built up is provided by table 3. This shows, on the one hand, which

units are common to all the alkaloids and, on the other, the respects in which the alkaloids differ from one another.

In the natural alkaloids themselves, the peptide chain cannot be open since (1) it possesses no free carboxyl group and (2) its composition corresponds to one molecule of water less than would be required by the open chain, probably because the carboxyl group of proline has taken part in the formation of a lactone ring.

As has already been observed, no definite information regarding the nature of the linkage between lysergic acid and the peptide portion is available. Investigations in this direction are being continued and a considerable number of peptides (21) of lysergic acid, isolysergic acid, and the three isomeric dihydrolysergic acids have been synthesized *via* the hydrazides and azides. The amino acids and peptides used in the preparation of these partially synthetic derivatives are shown in the following diagram:

*Peptide-like, partially synthetic derivatives of lysergic acid, isolysergic acid,
and dihydrolysergic acid*

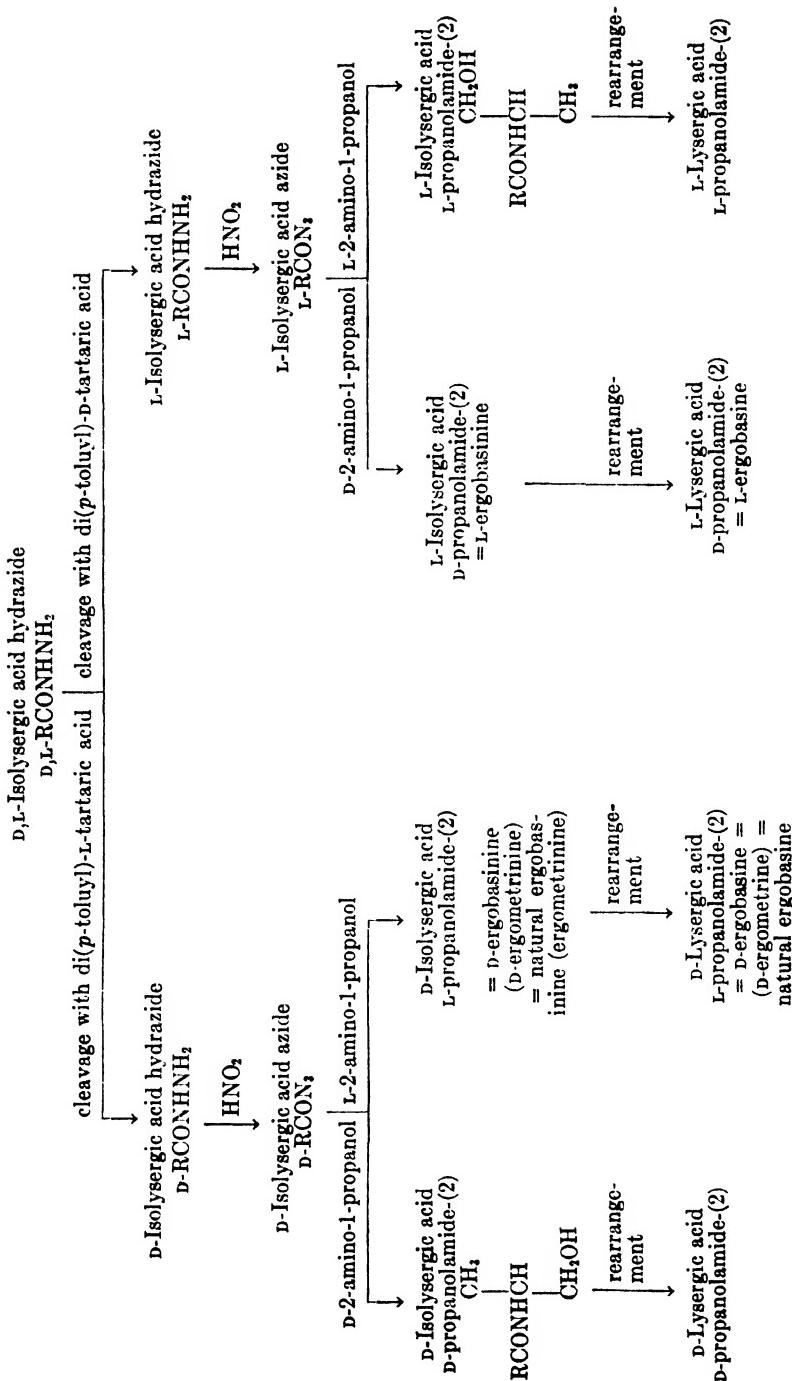


Unfortunately, none of these derivatives exhibited to an appreciable extent the sympatheticolytic and adrenolytic action so characteristic of the natural polypeptides of the ergot alkaloids.

It was mentioned at the beginning of this review that, apart from the five pairs of alkaloids of the polypeptide type which have just been discussed, ergot also contains an alkaloid of simpler structure, consisting of lysergic acid combined merely with L-2-amino-1-propanol and known as ergobasine or ergonovine. In contrast to the ergot alkaloids of higher molecular weight, this compound is soluble in water and can consequently readily be separated from the other alkaloids.

Shortly after Jacobs and Craig (6) had elucidated the structure of ergobasine, Stoll and coworkers succeeded in accomplishing its partial synthesis, and this still remains the only synthesis (17, 18) of a natural alkaloid (4, 10, 15, 27) of ergot which has so far been achieved.

Since lysergic acid, isolysergic acid, and the aminoalcohol each exist in two optically active forms, eight isomeric amides are theoretically possible; all of these have been prepared and characterized. The partial synthesis of these



compounds was accomplished in the following stages: Cleavage of natural ergot alkaloids of the peptide type with hydrazine hydrate provides a good yield of racemic isolysergic acid hydrazide, which can be separated through the di(*p*-tolyl)tartaric acid salt into the homogeneous optically active components, the hydrazides of *D*-isolysergic acid and *L*-isolysergic acid. On treatment with nitrous acid, the hydrazides are converted into the corresponding azides. These react similarly to acyl halides and, on condensation with the two homogeneous, opti-

TABLE 4
The eight isomers of ergobasine, C₁₉H₂₂O₂N₃

NAME	DECOMPOSITION POINT °C.	[α] _D ²⁰	TYPICAL CRYSTALLINE FORM
<i>D</i> -Lysergic acid <i>L</i> -propanolamide-(2) (<i>D</i> -ergobasine)	162	+90° (in water)	Well-formed tetrahedra from ethyl acetate; soft needles from benzene; very sparingly soluble molecular compound with 1 CHCl ₃
<i>L</i> -Lysergic acid <i>D</i> -propanolamide-(2) (<i>L</i> -ergobasine)	162	-89° (in water)	
<i>D</i> -Isolysergic acid <i>L</i> -propanolamide-(2) (<i>D</i> -ergobasinine)	196	+114° (in CHCl ₃)	From acetone in large transparent prisms
<i>L</i> -Isolysergic acid <i>D</i> -propanolamide-(2) (<i>L</i> -ergobasinine)	196	-115° (in CHCl ₃)	
<i>D</i> -Lysergic acid <i>D</i> -propanolamide-(2)	220	-11° (in pyridine)	From methanol on dilution with benzene in elongated flat prisms
<i>L</i> -Lysergic acid <i>L</i> -propanolamide-(2)	220	+10° (in pyridine)	
<i>D</i> -Isolysergic acid <i>D</i> -propanolamide-(2)	195	+353° (in CHCl ₃)	From acetone in massive prisms; perchlorate from 95 per cent alcohol in short prisms and polyhedra
<i>L</i> -Isolysergic acid <i>L</i> -propanolamide-(2)	195	-351° (in CHCl ₃)	

cally active 2-amino-1-propanols yield the four amides of isolysergic acid listed in table 4. On isomerization these are transformed into the corresponding derivatives of lysergic acid, one of which is natural ergobasine, *D*-lysergic acid *L*-propanolamide-(2). Some of the properties of the eight isomers are summarized in table 4.

Attention should be called particularly to the fact that corresponding antipodes possess precisely opposite optical rotations.

The crystalline forms of these eight isomers are shown in figure 2. From these photographs it may be clearly seen that the crystalline form of one member of any particular pair of isomers is the mirror image of that of the other.

The same process as was used for the synthesis of ergobasine has made possible the preparation of a whole series of homologous and analogous compounds (18). Moreover, these substances have been tested both on animals and in man, and interesting connections between the structures of the partially synthetic compounds and their pharmacodynamic actions have been established. A few of these compounds are summarized in table 5.

The most striking result which can be seen from table 5 is that only the derivatives of natural D-lysergic acid are active whereas the corresponding compounds obtained from L-lysergic acid are entirely without activity. On the other



FIG. 2. The eight isomers of ergobasine

1	D-Lysergic acid L-propanolamide (2) or D ergobasine (D ergonovine)
2	L-Lysergic acid D-propanolamide (2) or L ergobasine (L ergonovine)
3	D-Isolysergic acid L propanolamide (2) or D ergobasinine
4	L-Isolysergic acid D propanolamide (2) or L ergobasinine
5	D-Isolysergic acid D propanolamide-(2)
6	L-Isolysergic acid L propanolamide-(2)
7	D-Isolysergic acid D propanolamide-(2)
8	L-Isolysergic acid L propanolamide-(2)

hand, it makes no difference whatever to the activity whether the alcohol combined with lysergic acid is L- or D-2-amino-1-propanol. If the activity of ergobasine is taken as 1, then the activity of norergobasine is 0.3 and that of methylergobasine 1.5, whereas the activity of isopropylergobasine is again 0.3.

The last member of the series, lysergic acid diethylamide, likewise exerts a powerful action on the uterus but, at the same time, exhibits a remarkable effect on the human psyche (26). Even when administered orally, the very small dose of 30–50 γ is sufficient to cause marked psychic changes combined with hallucinations and colored vision. Similar phenomena are produced by mescaline but only in a dosage 2000 to 3000 times as great. These are only a few examples of the interesting pharmacological actions which have been observed with the partially synthetic derivatives of D-lysergic acid.

The action of the ergot alkaloids is influenced to a very large extent by the double bond in ring D of lysergic acid which, as already explained, is assumed to be in the 9,10-position. If this bond is saturated by catalytic hydrogenation, all the natural ergot alkaloids lose entirely their action on the uterus. On the other hand, the dihydroalkaloids of the polypeptide type exhibit a greatly enhanced

TABLE 5
Uterine action of ergobasine (ergonovine) and other lysergic acid amides

NO.	COMPOUNDS	ACTIVITY ON RABBIT UTERUS <i>in situ</i>
Isomers of ergobasine		
1.....	D-lysergic acid L-propanolamide-(2) (D-ergobasine, natural ergobasine)	1.0
2.....	L-Lysergic acid D-propanolamide-(2) (L-ergobasine)	0.0
3.....	D-Lysergic acid D-propanolamide-(2)	1.0
Homologs of ergobasine		
4....	D-Lysergic acid ethanolamide (norergobasine)	0.3
5.....	D-Lysergic acid (+)-butanolamide-(2) (methylergobasine)	1.3
6.....	D-Lysergic acid (+)-4-methylpentanolamide-(2) (isopropylergobasine)	0.3
Phenylergobasines		
7.....	D-Lysergic acid D-norephedrine	0.05 (approx.)
8.....	D-Lysergic acid L-norephedrine	1.0
9.....	L-Lysergic acid L-norephedrine	0.0
10.....	D-Lysergic acid D-nor-D-ephedrine	0.4
Various derivatives of ergobasine		
11.....	D-Lysergic acid 1,3-dihydroxypropanamide-(2) (hydroxyergobasine)	0.7
12.....	D-Lysergic acid L-N-benzylpropanolamide-(2) (N-benzylergobasine)	0.01 (approx.)
13.....	D-Lysergic acid L-ephedrine (N-methylphenylergobasine)	0.3
14.....	D-Lysergic acid diethylaminoethylamide	0.05 (approx.)
15.....	D-Lysergic acid diethylamide	0.7

sympathicolytic action, manifest by a pronounced antagonism to adrenaline, while their toxicity is greatly reduced in comparison with the natural products.

The alkaloids of the lysergic acid series yield only one dihydro derivative, whereas each of the alkaloids derived from isolysergic acid yields two derivatives corresponding to the dihydroisolysergic acids I and II. The dihydroalkaloids which have been prepared (20) are summarized in tables 6 and 7, together with some of their characteristic properties.

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BREDT'S RULE OF DOUBLE BONDS IN ATOMIC-BRIDGED-RING STRUCTURES

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I. INTRODUCTION

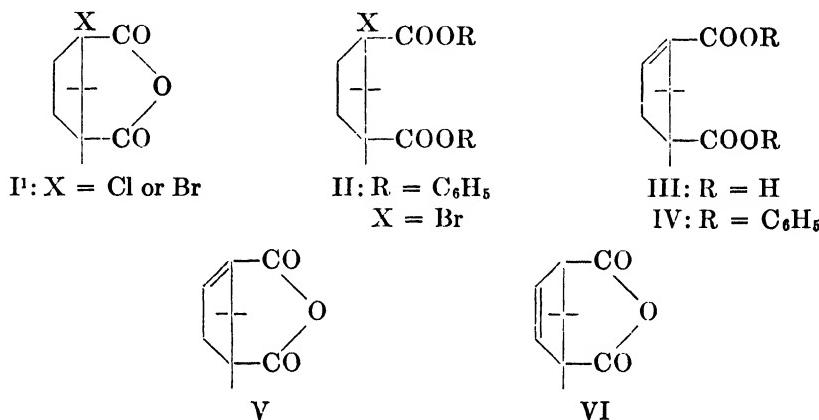
Bredt's rule is a qualitative generalization which describes structural limitations in bridged-ring compounds. From steric considerations Bredt concluded that certain bicyclic atomic-bridged-ring structures with a carbon-carbon double bond at a bridgehead atom should not be capable of existence. This rule has been useful in the determination of structure for terpene-like compounds and in the interpretation of reactions of bridged-ring compounds.

This review covers the literature on Bredt's rule from 1902 through May, 1950. Some work prior to 1902, which has been reinterpreted in terms of the rule, has been included. The examples described are ones in which the rule is referred to explicitly or implicitly, together with a few in which it can be used in interpreting the work reported. The literature has not been searched exhaustively but sufficient examples have been collected to illustrate the major points in the use of the rule.

II. ORIGIN OF BREDT'S RULE

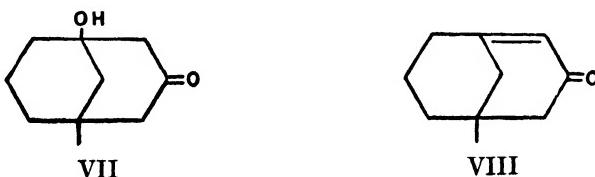
In 1902, Bredt, Houben, and Levy (39) compared the relative ease of dehydrohalogenating α -halocamphoric acid derivatives (I and II). It had previously been observed (12, 39) that α -bromocamphoric acid anhydride (I) was quite stable toward the removal of hydrogen bromide, being unchanged after heating with quinoline for 48 hr. It was found, however, that if the anhydride linkage was opened by conversion to the phenyl ester (II) the removal of hydrogen halide occurred readily to form IV. They further found that the unsaturated acid III

failed to form anhydride V, while the corresponding saturated compound readily cyclized. When dehydration of III was forced by distillation at atmospheric pressure there was obtained the anhydride (VI) of the isomeric acid, isodehydrocamphoric acid, having the double bond in another position. It was concluded that III cannot exist in the form of its monomeric anhydride, and Bredt offered the explanation that the hindrance of reactions leading to V was due to the stereochemical nature of these compounds.



As an explanation for the formation of tricyclic derivatives upon the dehydration of isoborneol and of camphenilic acid (*c.f.* page 237), Wagner and Brykner (177) in 1903 suggested that, because of stereochemical limitations, the formation of a double bond at a carbon atom common to two pentamethylene rings is hindered.

Rabe (132) in 1908 pointed out the extraordinary resistance of the β -hydroxyketone VII to dehydration (page 235). He explained this stability on steric grounds: ". . . the bicyclic system offers great resistance to the formation of a double bond in the [1,2]-position" (as in VIII). He did not mention the previous papers, although they had already been referred to by other workers (111).

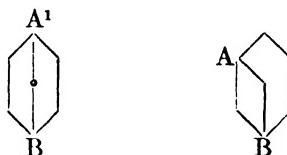


III. STATEMENT OF BREDT'S RULE

In the original reference (39) Bredt's rule was not stated formally. It was developed over a period of time in later investigations, particularly those of

¹ Many of the structural formulas have been drawn with a short line or with Me to indicate a methyl group; a heavy dot as used in the left-hand formula on page 222 represents a methylene bridge.

Bredt and coworkers. In considering specific structures they have indicated in a general way the type of compound in which, according to the rule, a double bond cannot occur, although no single discussion has covered all of the important features of the rule. Bredt's (44) statement of the rule in 1924 is typical of those which have been given: "On the basis of our conceptions of the positions of atoms in space, in the systems of the camphane and pinane series, as well as in similarly constituted compounds, a carbon double bond cannot occur at the branching positions A and B of the carbon bridge (the bridgeheads)."



Since it is inherently a qualitative rule, any simple statement will be indefinite about the borderline area. For the purpose of this discussion the rule may be stated as follows:

In polycyclic systems having atomic bridges, the existence of a compound having a carbon–carbon or carbon–nitrogen double bond at a bridgehead position is not possible, except when the rings are large, because of the strain which would be introduced in its formation by the distortion of bond angles and/or distances. As a corollary, reactions which should lead to such compounds will be hindered or will give products having other structures.

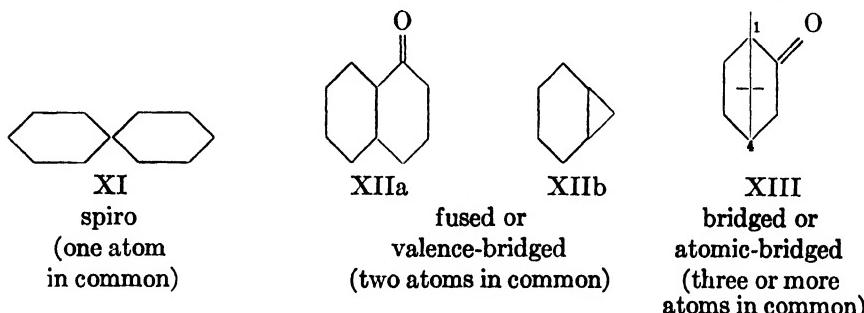
IV. NOMENCLATURE AND SCOPE OF BREDT'S RULE

For a typical atomic-bridged-ring compound such as camphor (XIII) the molecule may be considered to be made up of a ring which is spanned by a "bridge" of one or more atoms. The atoms of the large ring to which the bridge is attached (at positions 1 and 4 in XIII) are the bridgehead atoms and Bredt's rule applies to the stereochemistry of these bridgeheads. The concept of a bridge thus focuses attention on the large peripheral six-membered ring of the conventional planar projection, although for nomenclature XIII is regarded as a bicyclic structure made up of two contiguous five-membered rings.

A. BICYCLIC SYSTEMS

Bicyclic systems can be grouped into the types illustrated by formulas XI, XIIa, XIIb, and XIII. As far as Bredt's rule is concerned the nomenclature problem is to describe the kind of structure in which a bridgehead double bond is sterically improbable and to be consistent in stating and using the rule. According to nomenclature conventions (115) bicyclo [x.y.z] compounds are named in such a way that the numbers in the brackets are in decreasing order: i.e., $x \geq y \geq z$. Bredt's rule is regarded as applying only to structures having atomic bridges, i.e., to bicyclo [x.y.z] compounds in which $x \geq y \geq z \neq 0$. Structures

having a double bond at an atom common to two fused rings ($z = 0$), for example, the enol form of α -decalone XIIa (3d) or similar ring structures (139), are considered outside the scope of the rule. Those small valence-bridged-ring (fused-ring) structures having $z = 0$ in which a double bond at a carbon atom common to two rings would cause great strain—for example, XIIb—might be covered by other rules analogous to Bredt's rule. Nomenclature systems (3a, 43, 109, 115) differ in what is meant by the term “bridged-ring” and consequently the meaning of the term may be ambiguous. To avoid confusion the term “atomic-bridged-ring” is ordinarily used in this review; when the shorter term “bridged-ring” is used, it is intended to mean only structures having atomic bridges.



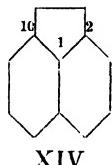
Bredt's rule applies to structures having double bonds involving either carbon or nitrogen but it is not certain whether it applies to a carbon–sulfur double bond (page 255). The rule apparently has not been used with other hetero atoms. It has been applied to systems in which the double bond is part of an aromatic ring. In such compounds, which effectively contain two bridgehead double bonds, the requirements of planarity and presumably the strain will be greater than with only one, but the resonance stabilization of the aromatic ring may tend to compensate for this (compare page 242). Hetero atoms in positions removed from the bridgehead apparently have no special influence.

In discussing the different possible positions for a substituent or a double bond in a bicyclo[$x.y.z$] compound—for example, bicyclo[3.2.1]octane—it is convenient to refer to a particular “branch” of the bicyclic system as the [3], the [2], or the [1] branch. A term S , defined by $S = x + y + z$, is used in discussing the total ring size of a bicyclic system; thus, in bicyclo[3.2.1]octane, $S = 3 + 2 + 1 = 6$.

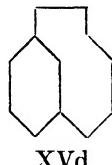
B. TRICYCLIC SYSTEMS

Many tricyclic systems in which all of the rings are not mutually contiguous can be treated as substituted bicyclic compounds. With three mutually contiguous rings, however, there may be some question about whether the rule applies to certain structures, since the criterion of the number of atoms in common needs qualification. Bredt (43) regarded perhydroacenaphthene (XIV) and similarly constituted structures as bridged-ring, considering, for example, C₁ as a bridge across the eleven-membered ring between C₂ and C₁₀, while Patterson (115) con-

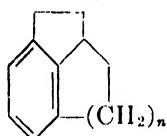
sidered XIV to be fused-ring, resulting from three ortho fusions (two atoms in common) among the three rings. Hückel (77b) included the unknown ring system XVa in a discussion of Bredt's rule and related topics. Compounds of this type with bridgehead double bonds are known where the rings are larger, for example, tetrahydroacenaphthene (XVb), and models do not indicate these to be unreasonably strained. The ring size of course is important here as with bicyclic



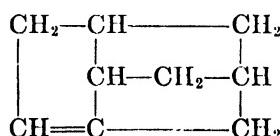
XIV
Perhydroacenaphthene



XVd



XVa: $n = 1$
XVb: $n = 2$



XVc

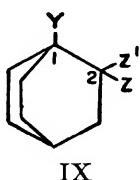
structures, although the critical value of a term analogous to S may be different from the value of S for a bicyclic system (*cf.* pages 223, 226). An approximate criterion of whether the rule permits or forbids a bridgehead double bond in a tricyclic structure such as XIV or XVb is to consider the smallest bicyclic analog from which it can be regarded as being derived by incorporation of an additional bond or bridge. A comparison of XIV with bicyclo[6.3.1]dodecane (XVd; $S = 10$, page 223), in which because of ring size Bredt's rule allows a bridgehead double bond, suggests that because of the ring size the rule should not prohibit such a bond in XIV. It seems logical that the rule be used to describe the impossibility of a bridgehead double bond in smaller-ring compounds like XIV even though each pair of rings has only two atoms in common. Such structures have many of the steric characteristics of their bicyclic analogs, and the presence of the additional bond or bridge would not be expected to reduce the amount of strain. Thus a compound having structure XVc (116), which might be derived from bicyclo[3.2.1]-5-octene by adding a carbon bridge, is regarded as prohibited by Bredt's rule (page 224). According to the rule a compound with the structure bicyclo[3.2.1]-5-octene ($S = 6$) is impossible, and the additional C₃-C₈ carbon bridge would hardly make the double bond less strained.

V. STEREOCHEMISTRY OF BREDT'S RULE

The condition which Bredt emphasized is the strain which would be present in a compound having both a small atomic-bridged-ring system and a bridgehead double bond. The rule has often been used in making a choice between structures suggested for a chemical compound. In other instances the hindrance

of a reaction has been explained by applying the rule to the expected product or to probable reaction intermediates. This type of steric hindrance can occur (a) with ring-closure reactions of unsaturated cyclic compounds which would form a bridged-ring system, and (b) in elimination or displacement reactions of bridged-ring compounds having substituents at or adjacent to the bridgehead position.

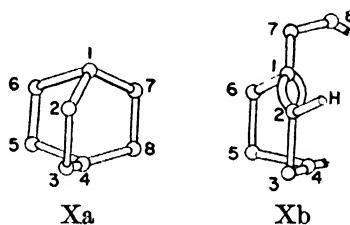
The cause of the hindrance in the ring closures can be regarded as the inability of the reactive groups to come within bond-forming distance of each other. Bredt (33) described the two carboxyl groups in III as being in positions intermediate between the *cis* and *trans* positions and used the term "*meso-trans*" to describe their relationship. Elimination or displacement reactions of bridged-ring derivatives may tend to give intermediate bridgehead carbonium ions, carbanions, or free radicals. In addition to their other special structural features, allylic- or benzylic-type bridgehead intermediates lack the resonance stabilization which is present with their open-chain or monocyclic counterparts (page 230), and consequently reactions which should involve them may be hindered. The groups which would participate in the elimination reaction may be so arranged that a *trans* elimination (54) is not facilitated, as in IX, where neither Z nor Z' is *trans* to the bridgehead substituent Y. Elimination is hindered (54) in certain structures in which the atoms involved are not in favorable positions, but there appears to be no basis for deciding the relative importance of this effect and the impossibility of the formation of the olefinic product which would result from elimination. The decarboxylation of β -keto acids (page 246) as well as some *cis* eliminations (2a) are considered to involve cyclic intermediates. While substituents at C₂ (IX) seem reasonably close to Y for the formation of such quasi-rings, the redistribution of the electrons to the 1,2-position to form an actual or a transient double bond as required for elimination or for enolization (page 249) would be hindered, according to Bredt's rule.



IX

The prohibitive strain which would be present in a small atomic-bridged-ring structure having a bridgehead double bond can be illustrated by means of models. The cyclohexane ring C₁-C₆ in Xa has bond directions at C₁ and at C₄ which will accommodate the C₇-C₈ bridge without appreciable strain. With a carbon-carbon double bond at C₁-C₂, however, the preferred bond direction from C₁ is no longer one which will permit a two-membered bridge to reach C₄ without considerable difficulty. Carbon atoms C₁ and C₂ and the four atoms attached (C₃, C₆, C₇, and H) all must lie in a common plane if the system is to be strainless. Woodward and Kovach (201) considered that Bredt's rule follows as a simple corollary from this principle as applied to small bicyclic systems. Freudenberg

berg (66) interpreted Bredt's rule as meaning that the two substituents attached to one of the carbon atoms of a carbon-carbon double bond cannot lie on the same "side" of the double bond, i.e., the same side of the plane through C₁ and C₂ suggested by the curved bonds in Xb. Prelog (123) interpreted the rule as describing the conditions necessary for effective overlap of the *p*-electron orbitals constituting the π -bond of the double bond (*cf.* page 227). If the unsaturated bridged-ring structure pictured by Xb were to be formed by closing the C₄—C₈ bond, a large amount of energy would be required in distorting bond angles and/or distances and the resulting structure would be highly strained. Bartlett



and Knox (20) estimated that such a structure with a bridgehead double bond would be less stable than the isomer with a C₂—C₃ double bond by approximately 22.5 kcal. per mole and thus the probability of the existence of the former is quite low. The 1,2-double bond and the small bridged-ring system are thus mutually exclusive.

A long chain of carbon atoms from C₁ is able to reach C₄ without great strain, even with the C₁—C₂ double bond (Xb); hence the rule does not prohibit a bridgehead double bond in bridged rings of unlimited size. The rule, however, does not divide ring sizes sharply into those where a bridgehead double bond is possible and those where it is not possible, since insufficient experimental data have been obtained in the borderline area. There will be intermediate ring sizes, different bridgehead positions with a given ring size, or transient reaction intermediates where the possibility of a bridgehead double bond cannot be predicted. According to ball-and-peg models, in a bicyclo[x.y.z]alkene ($x \geq y \geq z \neq 0$) structures with a double bond at a bridgehead can be made strainlessly when $x + y + z = S = 11$. Many structures with a bridgehead double bond can be formed with little strain when $S = 10$, some even with $S = 9$, but with $S = 8$ the strain is quite large. Bredt (34) concluded that bicyclo[4.4.1]-1,6-undecadiene ($S = 9$), having a double bond at each bridgehead in the [4] branches, can be constructed from models almost strainlessly, while considerable strain is present when a double bond lies in the [1] branch, as in bicyclo[4.4.1]-11-undecene (compare Section VI, C, page 248). From a study of bicyclo[x.3.1]alkenones Prelog and coworkers (123, 124, 127) (table 1) concluded that $x = 5$ ($S = 9$) represents the smallest ring size where a bridgehead double bond can occur in an isolable compound. The conclusions from models thus appear to correspond reasonably well with the observed structures, i.e., with $S = 9$ a bridgehead double bond is possible. The tentative upper limit to the ring size for which the rule forbids such

double bonds in isolable compounds is $S = 8$. For a transient reaction intermediate such as is thought to occur in the decarboxylation of β -keto acids this limit is probably lower, tentatively at $S = 6$ (page 248).

Attachment at C₂ or at C₆ in X_b to form a bicyclo[4.*n*.0]alkene valence-bridged-ring (fused-ring) structure, while requiring some distortion of bond angles when closing a small ring, does not involve such a drastic change of bond direction as in forming a bicyclo[3.*n*.1]alkene or a bicyclo[2.*n*.2]alkene bridged-

TABLE 1
Formation of bicyclic compounds by intramolecular aldol condensation
(Prelog and coworkers)

STARTING MATERIAL		PRODUCT				REFERENCE
Structure	<i>n</i>	Bridged (B) or fused (F)	Bicyclic system [x.y.z.]	S ($x+y+z$)	Double bond(s)	
LXX ^(a)	3	F	[4.4.0]		α,β	(127)
	4	F	[5.4.0]		α,β	(127)
	5	Mixture	[6.4.0]		α,β	(127)
			B	9	α,β	(127)
			[6.3.1]	10	α,β	(127)
			[7.3.1]	11	α,β	(127)
			[12.3.1]	16	α,β	(127)
LXXIII ^(b)	3	B ^(c)	[3.3.1]	7	β,γ	(124)
	4	B ^(d)	[4.3.1]	8	β,γ	(124)
	5	B ^(d)	[5.3.1]	9	α,β	(124)
	10	B ^(e)	[10.3.1]	14	α,β	(124)
LXXVIa ^(f)	3	F	[4.4.0]		Aromatic	(125)
	4	F	[5.4.0]		Aromatic	(125)
	5	B	[5.3.1]	9	Aromatic	(125)
	6	B	[6.3.1]	10	Aromatic	(125)
	10	B	[10.3.1]	14	Aromatic	(130)
	12	B	[12.3.1]	16	Aromatic	(125)

^(a)Decarboxylation occurred in condensation, yielding a bicyclic ketone.

^(b)Product was a β -keto ester.

^(c)The β -keto acid was not decarboxylated on heating with quinoline at 240°C.

^(d)Decarboxylation of the β -keto acid occurred on heating with quinoline at 240°C.

^(e)Decarboxylation occurred on saponification of the β -keto ester.

^(f)Product was an aromatic derivative (phenol).

ring structure. These fused-ring structures are considered to be outside the scope of Bredt's rule.

The structure of ethylene has been described (53, 72d, 117) as a planar arrangement with three orbitals (*s*, *p*_{*x*}, and *p*_{*y*}) of each carbon atom lying in a plane and hybridized to form three *sp*² bond orbitals with their bond directions (σ -bonds) in the plane. The fourth orbital (*p*_{*z*}) of each carbon atom has a node in the plane and lobes extending above and below the plane, and the two *p*_{*z*} orbitals

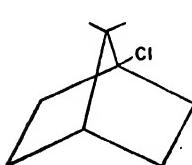
of the adjacent carbon atoms, having electrons with opposite spins, overlap laterally to form what amounts to the second bond (π -bond) of the double bond. The maximum overlapping of the p_z orbitals occurs when they are parallel, i.e., when all six of the atoms are coplanar, and this interaction restricts rotation about the carbon-carbon axis. Prelog, Barman, and Zimmermann (124) considered that if a bridgehead double bond did occur in a small atomic-bridged-ring system the bridgehead carbon atom would deviate greatly from the planar trigonal σ -electron arrangement which is preferred in an ordinary double bond. Since the form and spatial arrangement of the p_z orbital can be altered to only a limited extent, such a steric situation would lead to an uncoupling of the π -electron system of the double bond and therefore to an increase in the energy level, that is to a decrease in stability. Their view was that the facts which are described by Bredt's rule constitute examples of the steric hindrance of the resonance of the two π -electrons of a double bond and thus belong to the simplest case of steric hindrance of resonance electrons which is often found with conjugated systems. It seems likely that if unsaturation should occur at a bridgehead position in a relatively small bridged-ring system a normal double bond would not exist, but that diradical and/or dipolar forms would contribute greatly to the state of the molecule (69).

Bredt's rule has been used primarily with carbocyclic compounds where, in general, the saturated atoms have a tetrahedral configuration and two doubly bound atoms and their four substituents are coplanar. Wittig (197b) considered that the rule should also be applicable to nitrogen compounds, since this atom when tetravalent has a tetrahedral configuration similar to that of carbon, and the observations with a number of nitrogen-containing structures seem to justify this extension of the rule (cf. page 258). Doering and Levy (59) suggested that the rule may not apply to a carbon-sulfur double bond where there is the possibility of octahedral bond angles, but this question was not answered by the available data (cf. page 255).

VI. APPLICATIONS OF BREDT'S RULE

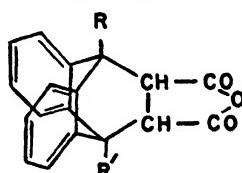
A. DEHYDROHALOGENATION REACTIONS

1. Bicyclic compounds having halogen at the bridgehead position



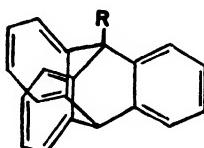
XVII

1-Chloroapocamphane



XVIII: R = Br, R' = H

XVIIIa: R = R' = Cl

XVIIIb: R = R' = C₆H₅

XIXa: R = Br

XIXb: R = H

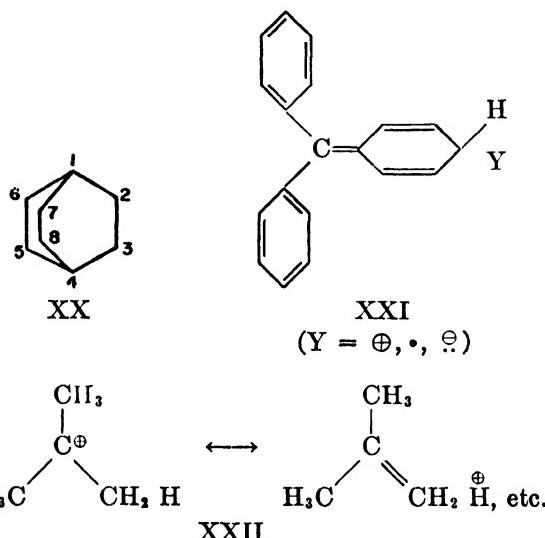
- (a) 1-Chloroapocamphane, 9-bromo- and 9,10-dichloro-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid anhydride, and 1-bromotriptycene

Bartlett and coworkers (19, 20, 21, 23) studied several bicyclic bridged-ring compounds having a bromine or chlorine substituent at the bridgehead position and found these halides to be extremely inert. When 1-chloroapocamphane (XVII) was heated for 21 hr. with 30 per cent potassium hydroxide in 80 per cent ethanol, it was recovered unchanged (20). When it was heated at the boiling point with silver nitrate in water-ethanol solution for 48 hr., conditions which might be expected to cause reaction *via* a carbonium-ion intermediate (72b), the solution remained clear with no opalescence and the starting material was again recovered. (Compare the reported replacement of OH by Cl in [3.3.1] system, page 236.) The similarly substituted halides diethyl *tert*-butylcarbinyl chloride and bornyl chloride in contrast were found to be quite reactive. The dibenzobicyclooctane derivative XVIII, previously found by Barnett, Goodway, Higgins, and Lawrence (17) to be stable toward dehydrohalogenation, showed no replacement of the halogen on boiling for 18 hr. with 21 per cent potassium hydroxide (19). Similarly, 1-bromotriptycene (XIXa), in sharp contrast to triphenylmethyl halides, formed a colorless nonconducting solution in liquid sulfur dioxide. The bromine was unreactive when XIXa was heated in toluene solution with stannic chloride under conditions which produced chloroanthracene from anthracene dibromide. Bartlett and Lewis (21) considered these experiments to demonstrate that the positive triptycyl ion, if it exists at all, cannot be formed by methods applicable to analogous triaryl methyl compounds. No reaction was observed when 1-bromotriptycene was treated with copper powder, with zinc dust, or with molecular silver, the latter even at 280°C. in mineral oil. Reaction occurred slowly with sodium or with magnesium to form triptycene (XIXb), but attempts to isolate intermediate organometallic derivatives or carbonation products were not successful. It was concluded that if a free-radical intermediate occurs in this reaction, this triptycyl free radical must be more reactive toward hydrogen in the hydrocarbon solvent than ordinary aliphatic free radicals, thus differing markedly in stability from analogous triaryl methyl free radicals, in which resonance stabilization (118) can occur (see formula XXI). The low reactivity of these atomic-bridged-ring derivatives and the instability of the triptycyl free radical were accounted for by the steric limitations imposed by the ring system upon the bridgehead carbon atom (*cf.* "active" hydrogen in triptycene and the triptycyl carbanion, page 254).

Bartlett and Knox (20) explained the fact that dehydrohalogenation of 1-chloroapocamphane (XVII) did not occur by applying Bredt's rule to the cycloolefin which should be formed, and the circumstances with XVIII are comparable. They estimated that the bridgehead olefin bicyclo[2.2.2]-1-octene is more strained than the -2-octene isomer by approximately 22.5 kcal. per mole, indicating that here Bredt's rule is well justified thermodynamically. Rearrangement of the system into one capable of olefin formation, with accompanying inversion of carbon atom 1, is subject to the same kind of steric limitations as direct displacement (18, 22).

Some reactions of alkyl halides—for example, reaction of arylated methyl halides or of tertiary alkyl halides with silver nitrate—are considered to occur

with the formation of intermediate solvated carbonium ions (72b, 166). A large amount of evidence indicates that these carbonium ions must be essentially planar. Bartlett and Knox (20) estimated that a strain of approximately 22.5 kcal. per mole would be required to force carbon atom 1 into the plane of atoms 2, 6, and 7 in the bicyclo[2.2.2]octane system (XX), and an even greater amount would be necessary in the apocamphane ring; hence ionization of these halides is greatly hindered. In compounds such as triphenylmethyl bromide ionization is facilitated, since the carbonium-ion intermediate is stabilized by the contribution of several resonance forms (XXI) which, ideally, require coplanarity of the rings and the central carbon atom. With the ion from the bridgehead halides, analogous structures would require a bridgehead double bond, and Bartlett and



Cohen (19) considered that according to Bredt's rule they cannot contribute significantly to the resonance. In view of Swain's (166) recent work on the importance of the solvation of ionic reaction intermediates, Bartlett and Lewis (21) regarded it as an open question whether these resonance effects or the lack of solvation due to shielding by the bridged-ring system is the more important factor in the unreactivity of these halides. One may consider that hyperconjugative resonance structures such as XXII generally contribute to the stability of a tertiary carbonium ion, but if the central atom is a bridgehead, as in XVII, the occurrence of analogous forms also would be hindered.

Clar (2, 47) attempted to dehydrohalogenate XVIIIa, obtained by the Diels-Alder condensation of 9,10-dichloroanthracene and maleic anhydride, by heating it with quinoline. He considered that the removal of 2 moles of hydrogen chloride should give a substance which would be formed in disagreement with Bredt's rule or which would be a free diradical. The product obtained, however, was 9,10-dichloroanthracene, the thermal reversal of the Diels-Alder condensation taking

place in preference to the dehydrohalogenation. Clar (2, 47, 169) further observed that XVIIIa easily reacted with benzene in the presence of aluminum chloride, while the halogens in 9,10-dichloroanthracene were found to be inert in Friedel-Crafts syntheses. The product obtained was 9,10-diphenylanthracene and thus cleavage of the bridge, which took place on heating XVIIIa alone, occurred here also. It was considered that the reaction of 9,10-dichloroanthracene with maleic anhydride to form XVIIIa deprives the carbon atoms in the 9- and 10-positions of their aromatic character, thus increasing the reactivity of the chlorine atoms and making them replaceable, and XVIIIb was postulated as an intermediate in the Friedel-Crafts conversion of XVIIIa to 9,10-diphenylanthracene. In view of the work described above and the fact that the bridged-ring system is not preserved, it seems unlikely that it is in the original atomic-bridged-ring system XVIIIa that the halogens are reactive.

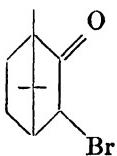
(b) α -Halocamphoric acid anhydrides

The earliest mention of what is now known as Bredt's rule was made by Bredt, Houben, and Levy (39) in a discussion of the dehydrohalogenation of α -halocamphoric acid derivatives (cf. page 220).

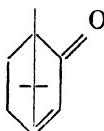
2. Bicyclic compounds having halogen adjacent to the bridgehead position

(a) 3-Bromocamphor

Schiff (142; see also 55) found that 3-bromocamphor (XXIII) on treatment with alcoholic potassium hydroxide unexpectedly gave camphor, and presumably potassium hypobromite. It was found (12) also that 3-bromocamphor could be heated with aniline or with quinoline without removal of hydrogen bromide, except for a small amount attributed to resinification, the bulk of the bromocamphor being recovered. This behavior could not be accounted for adequately by simple analogy with open-chain compounds, and in attempting to do so Aschan (12) doubted Bredt's structure for camphor on which that shown for the bromide is based.



XXIII
3-Bromocamphor



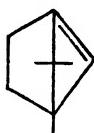
XXIV

Bredt (44) explained these observations by calling attention to the fact that XXIII cannot split out hydrogen bromide to form the unsaturated ketone XXIV because here the double bond would lie at a bridgehead.²

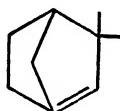
² Apparently the Favorskii rearrangement of the α -bromoketone XXIII also is hindered. Extensive decomposition occurred, possibly preceded by elimination reactions, rather than ring contraction to the expected strained cyclobutane derivative, in the attempted Favorskii rearrangement of 2-chlorocyclopentanone (64). Compare the pinacol rearrangement of *trans*-1,2-dimethyl-1,2-cyclopentanediol (18, 105).

(b) "Camphenilyl chloride"; structure of "camphenilene"

An unsaturated hydrocarbon C_9H_{14} , designated "camphenilene,"³ has been reported in several investigations to be obtained from camphenilol (XXXII) (*a*) by conversion to "camphenilyl chloride" (regarded as having structure XXXIII) with phosphorus pentachloride followed by dehydrochlorination with amines or sodium alkoxides and (*b*) by dehydration with potassium bisulfate. Several structures, including XXVI, XXVII, and XXVIII, which have been proposed (74, 79, 150, 158) for "camphenilene" are inconsistent with Bredt's rule.



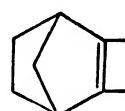
XXVI



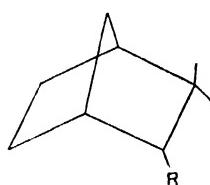
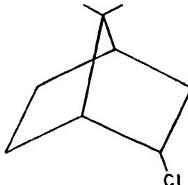
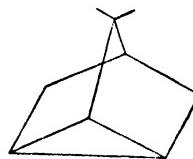
XXVIII



XXVII

XXIX
Santene

On the basis of this rule Meerwein (104a) criticized structure XXVIII, which Hintikka and Komppa (74) had proposed for the product obtained by route (*a*), and his suggestion that the material which they actually obtained was santene (XXIX) was confirmed by Komppa and Hintikka's (89, 90) reinvestigation, using routes (*a*) and (*b*). A mixture usually has been obtained and apobornylene (7,7-dimethylbicyclo[2.2.1]-2-heptene) and apocyclene (XXX) have been reported as other components. Structure XXVIII was revived by Snitter (158; cf. also 85) from an investigation of the Raman spectra of the materials obtained by routes (*a*) and (*b*), and it was again criticized according to Bredt's rule by Gratton and Simonsen (68), by Komppa and Nyman (91), and by Lipp and Daniels (98). The "camphenilyl chloride" was considered (81a, 91, 98) to be a mixture containing an apobornyl chloride (α -fenchocamphoryl chloride) (XXXI), and the problem is further complicated because the investigators used different reagents in the dehydrohalogenation reaction. Although it has been suggested

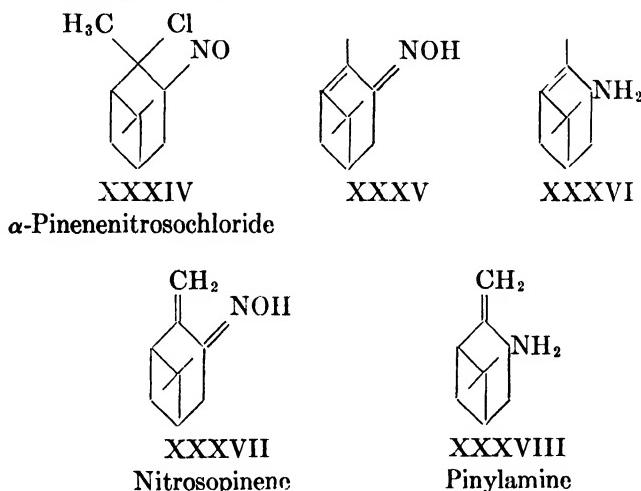
XXXII: R = OH
XXXIII: R = ClXXXI
 α -Fenchocamphoryl
chlorideXXX
Apocyclene

³ The name "camphenilene" has also been used for 5,5-dimethylbicyclo[2.2.1]-2-heptene obtained, for example, by the dehydration of 5,5-dimethylbicyclo[2.2.1]-2-heptanol via the methyl xanthate ester (112).

(155d) that a small amount of "camphenilene" (structure XXVIII) might actually be present, since ozonolysis apparently gave a small amount of an unidentified ketoaldehyde, there seems to be no satisfactory evidence to support structure XXVIII as an exception to Bredt's rule.

(c) α -Pinenenitrosochloride; structure of nitrosopinene and its derivatives

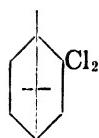
α -Pinenenitrosochloride, XXXIV (or dimeric structure), when treated with basic reagents such as alcoholic potassium hydroxide, loses hydrogen chloride to form a product, $C_{10}H_{16}NO$, designated nitrosopinene (171). Of the various structures proposed for nitrosopinene XXXV seems to have been accepted (141, 178, 180, 181) along with structure XXXVI for pinyllamine, which is obtained from nitrosopinene by reduction with sodium and ethanol or with zinc



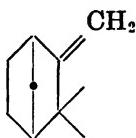
and acetic acid. Ruzicka and Trebler (141) criticized these structures on the basis of Bredt's rule; their reinvestigation showed nitrosopinene to have structure XXXVII and pinyllamine the corresponding structure XXXVIII, thus being derivatives of β -pinene. Pinocarvone oxime, usually regarded as having structure XXXVII, was considered by Ruzicka and Trebler to be stereoisomeric with nitrosopinene, but in more recent work Schmidt has concluded that the substance previously described as pinocarvone oxime is actually the oxime of myrtenal (*cf.* under carvopinone, page 262).

(d) α -Camphor dichloride and camphenilone dichloride

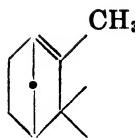
When dehalogenated by means of sodium, α -camphor dichloride (XXXIX) was reported (83) to form XL, and the product obtained similarly from camphenilone dichloride (XLI) was found (74) to be XLII. Meerwein (104b) pointed out that in these reactions the two probable primary hydrocarbon products XLIII and XLIV, respectively, are unstable and have a tendency to change over to a more stable form by displacement of the double bond. It seems probable



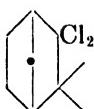
XXXIX



XL



XLIII

 α -Camphor dichloride

XLI



XLII

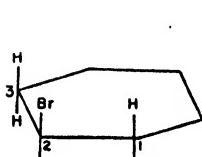
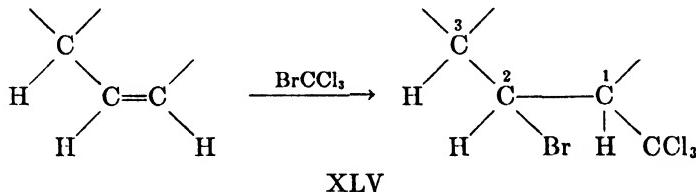


XLIV

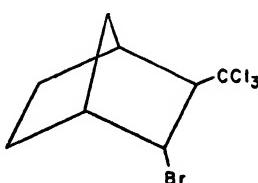
that XLIII and XLIV are never actually formed but that in each reaction the product-determining step is the removal of a hydrogen from a reaction intermediate with the formation of the double bond and that the loss of the hydrogen is favored in that direction which will give the olefin having the least strain.

(e) 2-Bromo-3-trichloromethylbicyclo[2.2.1]heptane, 2-bromo-3-trichloromethylbicyclo[2.2.2]octane, and 6(or 5)-bromo-5(or 6)-trichloromethyl-3a,4,5,6,7,7a-hexahydro-4,7-methanoindene

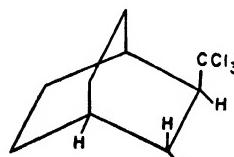
In studying the reactivity of olefinic double bonds in free-radical addition reactions Kharasch and Friedlander (84) obtained products of the type of XLV from various olefins and bromotrichloromethane. Adducts were obtained with open-chain, monocyclic, and bicyclic atomic-bridged-ring olefins and these three classes of addition products showed different behavior toward the dehydrohalogenating reagent alcoholic potassium hydroxide. With the open-chain compound derived from 1-octene the bromine was removed with a hydrogen from C₁ to form a trichloromonoene; with the monocyclic adduct derived from cyclohexene the bromine was removed with a hydrogen from C₃ and also a chlorine



XLVIII



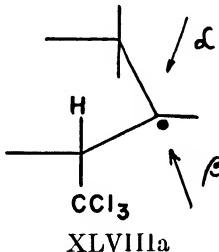
XLVI



XLVII

was removed with hydrogen from C₁ to form a dichloro conjugated diene; the bridged-ring derivatives, however, were quite resistant to the loss of hydrogen halide. XLVI did not react when heated at 50°C. with 0.7 N potassium hydroxide in absolute ethanol for 6 hr. Kharasch and Friedlander explained this stability of the bicyclic compounds XLVI, XLVII, and the dicyclopentadiene addition product by the use of Bredt's rule, since elimination of the bromine with hydrogen from C₃, as occurs with the monocyclic compounds, would require a double bond at a bridgehead, and the elimination with hydrogen from C₁ would not occur readily in view of the behavior of the monocyclic adducts described above.

The observed direction of elimination with the monocyclic adducts and the stability of the bicyclic derivatives suggest that *trans* addition of the bromine and trichloromethyl groups occurs as shown in XLVII and XLVIII, for then the hydrogen atom on C₁ would not be in the proper position for the preferred process of *trans* elimination of hydrogen bromide (54). It seems probable that the bromo-trichloromethane molecule would approach the radical intermediate XLVIIIa from the direction α , rather than β , in order to remain farther removed from the —CCl₃ group (72a).



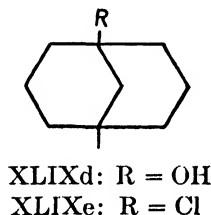
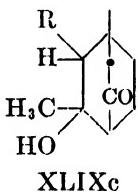
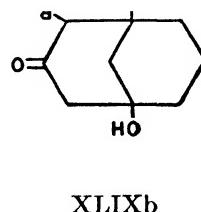
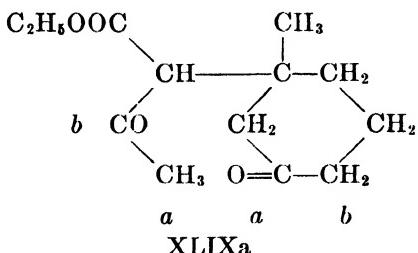
B. DEHYDRATION REACTIONS

1. Bicyclic compounds having hydroxyl at the bridgehead position

(a) Substituted bicyclo[3.3.1]-1-nonanol-3-ones

Rabe (132) investigated the cyclization of the diketo ester XLIXa and obtained (after hydrolysis of the ester group) a bicyclic β -hydroxyketone which was remarkably stable toward dehydration (cf. page 221). He considered that, depending on the manner in which the ring closure occurred, either a bicyclo[3.3.1]nonane derivative XLIXb (ring closure through groups *a—a*) or a bicyclo[2.2.2]octane derivative XLIXc (ring closure through groups *b—b*) would be formed. Rabe favored the bicyclononane structure (XLIXb) on the basis of strain considerations, assuming a planar cyclohexane ring in XLIXa. Ruzicka (137) called attention to the fact that, according to Bredt's rule, dehydration of a compound having structure XLIXb should not occur readily because this would form a double bond at the bridgehead. After the introduction of the concept of a strainless nonplanar cyclohexane ring, Mohr (110) pointed out that formation of either structure XLIXb or XLIXc should be possible without steric difficulties and that XLIXb was not necessarily favored, as Rabe had

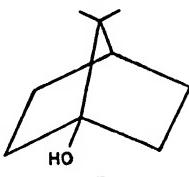
assumed. He suggested that further experimental proof was needed. In later work Rabe and Appuhn (131) obtained additional data to support the bicyclo-nonane structure XLIXb. They felt that although, according to Bredt's rule, either structure accounted for the resistance of the β -hydroxyketone to the facile dehydration which is typical of nonbridged β -hydroxyketones, the stability of the monocarbinol obtained on reduction of the carbonyl group was best explained by assuming structure XLIXb. The carbinol (XLIXd) resisted dehydration on heating with zinc dust at 230°C. or on heating the xanthate ester, and the



chloride (XLIXe) obtained from the carbinol and phosphorus pentachloride failed to eliminate hydrogen chloride when heated at the boiling point (193°C.) with dimethylaniline. Rabe and Appuhn considered the stability of these compounds according to Bredt's rule as convincing evidence in favor of the bicyclo-nonane structure XLIXb, which would lead to the indicated derivatives with the hydroxyl and chlorine groups at the bridgehead position. If the carbinol were derived from XLIXc it could presumably undergo dehydration by loss of a non-bridgehead hydrogen.

(b) 1-Apocamphanol

Bartlett and Knox (20) found that 1-apocamphanol (L), in spite of being a tertiary alcohol, dissolved reversibly with no evidence of reaction in concen-



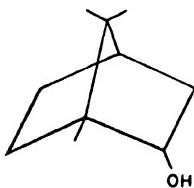
1-Apocamphanol

trated sulfuric acid. This suggested to them that dehydration and molecular rearrangement leading to dehydration are prohibited in this compound, as one should expect from Bredt's rule and other considerations (20) concerning rearrangement (*cf.* 1-chloroapocamphane, page 228).

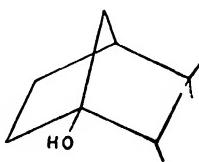
2. Bicyclic compounds having hydroxyl adjacent to the bridgehead position

(a) "Isoborneol" and camphenilic acid

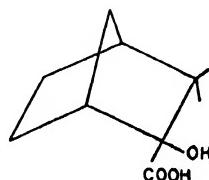
Shortly after Bredt first discussed the problem of dehydrocamphoric acid anhydride Moycho and Zienkowsky (111) described their work with isoborneol (LI) and camphenilic acid (LII). Under the assumption that the structure of isoborneol was LIII, they pointed out that in these two structures simple dehydration would lead to a double bond at a bridgehead in disagreement with Bredt's rule. One product from the dehydration of isoborneol is cyclene, and from the assumed structure for the former and Bredt's rule they suggested that LIV could be the structure of cyclene, the dehydration occurring so as to form a new three-membered ring. Since the structures of isoborneol (LI) (81c) and cyclene (LV) are now considered to be different from those assumed by Moycho and Zienkowsky, this application of Bredt's rule is of limited interest. Dehydration for such a structure (LIII) as they assumed for isoborneol should be similar to that for 1-apocamphanol (I), discussed by Bartlett and Knox (20). From camphenilic acid (LII) the products were reported to be dehydrocamphenilic acid (tricyclenic acid; LVI) (*cf.* page 261) and an unsaturated hydrocarbon "camphenilene" (santene (XXIX)), the reaction apparently being similar to the dehydration of the structurally similar camphenilol (page 232).



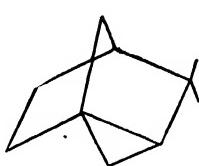
LI
Isoborneol



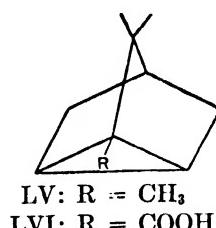
LIII



LII
Camphenilic acid



LIV



LV: R = CH₃
LVI: R = COOH

(b) Camphenilol

See the dehydrohalogenation of "camphenilyl chloride" (page 232).

(c) Epiborneol

The dehydration of epiborneol (LVII) by heating the methyl xanthate ester was found by Bredt and Perkin, Jr., (40, 41) to give bornylene (LVIII). That LVIII is formed rather than the strained dehydrocamphane (LIX) was cited by Bredt (44) in support of the rule.



Epiborneol
LVII



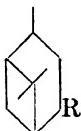
Bornylene
LVIII



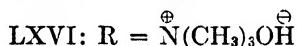
Dehydrocamphane
LIX

(d) Verbanol

Dehydration of verbanol (LXV) by heating the methyl xanthate ester was reported by Wienhaus and Schumm (188) to give δ -pinene (LXII). The same product was obtained (187) by the Hofmann exhaustive methylation of verbanylamine *via* its quaternary ammonium hydroxide (LXVI). It was pointed out (168b) that these elimination reactions can go in only this one direction if the



LXV: R = OH



pinane ring system is to remain intact.

(e) Verbenol

Blumann and Zeitschel (29, 30) reported the diene verbene, obtained by dehydration of verbenol (LX) with acetic anhydride, to have structure LXI. Reduction of verbene with sodium and alcohol forms dihydroverbene which they considered to be LXII, although the properties of the hydrocarbon and several of its derivatives were observed to be quite similar to the properties of α -pinene (LXIII) and its derivatives. Ruzicka and Trebler (138, 141) called attention to the fact that the proposed structure LXI is in conflict with Bredt's rule, and the alternative structure LXIV was suggested for verbene. It was concluded



Verbenol
LX



LXI



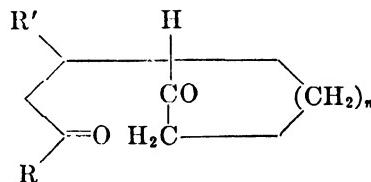
δ -Pinene
LXII



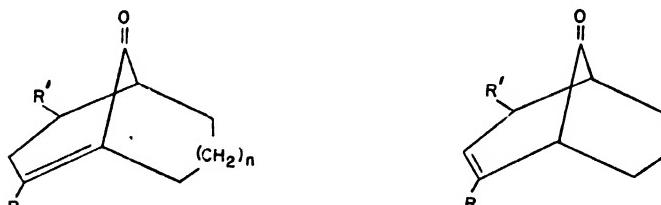
that the dihydroverbene obtained by reduction was actually α -pinene (LXIII). Structure LXIV for verbene was further supported by an investigation (60) of its Raman spectrum, and this structure (LXIV) has been recorded in later compilations (25a, 81b).

(f) Substituted 2-hydroxybicyclo[n.3.1]- ω -alkanones ($n = 3-12$)

Stobbe and coworkers (67, 163, 164) prepared several unsaturated bicyclic ketones by the intramolecular aldol condensation of monocyclic 1,5-diketones of the type of LXVII, and they assumed the double bond formed on dehydration of the intermediate aldols to be at the bridgehead position as in LXVIII. The position of the double bond in LXVIIIa was questioned by Mohr (110), who referred to Bredt's rule. Allen and Sallans (6) repeated some of Stobbe's work and extended it to other analogs, including LXVIIIb (or LXIXa), in which they also assumed the bridgehead position for the double bond. In reviewing this work Allen (3e) pointed out that this location is contrary to Bredt's rule, but on the basis of the indirect evidence available at the time he concluded that these substances constitute exceptions to the rule. It was again pointed out (81d) that structures like LXVIII would be highly strained, if not altogether impossible. An investigation (50) of the ultraviolet absorption spectra of the diphenyl-substituted unsaturated ketone LXVIIIb (or LXIXa) and some related



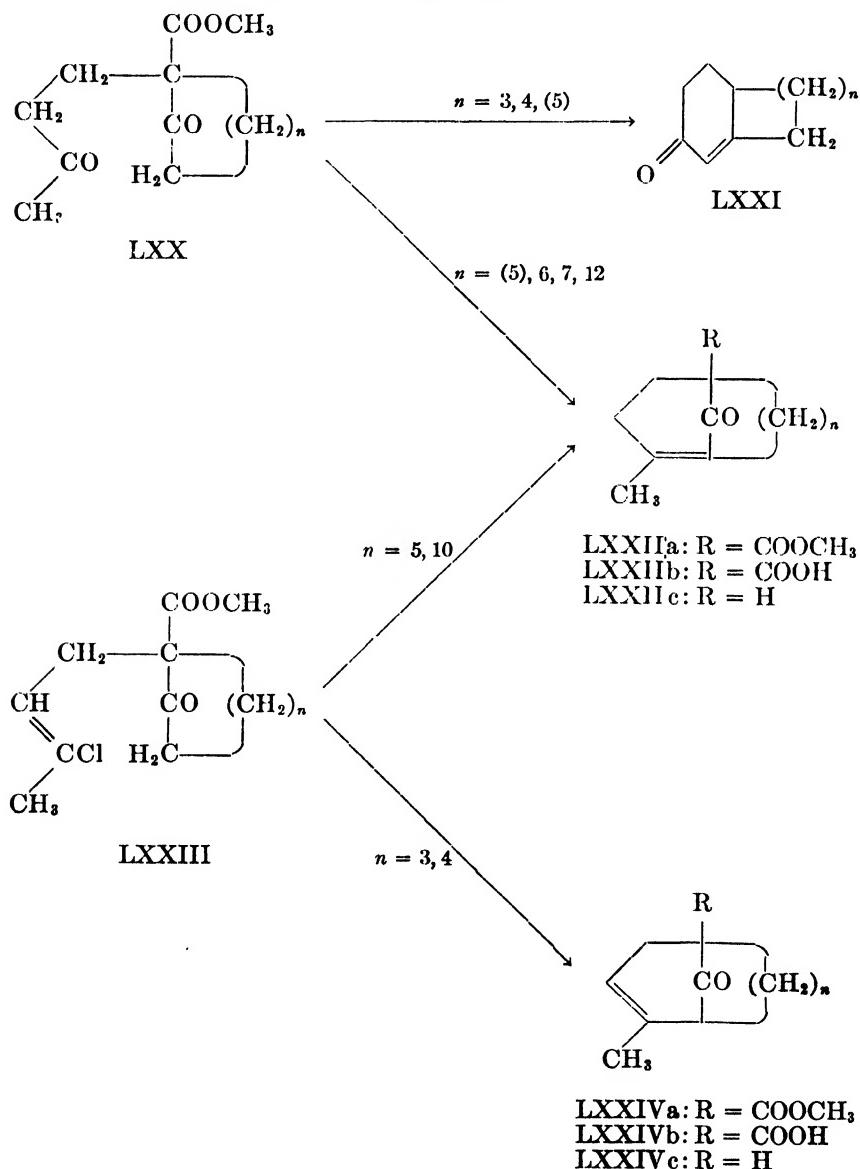
LXVII: $n = 0, 1$; $R = R' = C_6H_5$



LXVIIIa: $n = 0$; $R = R' = C_6H_5$
 LXVIIIb: $n = 1$; $R = R' = C_6H_5$
 LXVIIIc: $n = 1$; $R = C_6H_5$; $R' = H$

LXIXa: $R = R' = C_6H_5$
 LXIXb: $R = C_6H_5$; $R' = H$

compounds has provided evidence that the double bond is not in the α,β -(bridgehead) position. With the alternative structure LXIXa having a β,γ -double bond, therefore, this compound (and presumably the other small-ring ones prepared in the same way) does not appear to be an exception to Bredt's rule. The related monophenyl-substituted unsaturated ketone similarly was shown (51) by means of the ultraviolet absorption spectrum of its 2,4-dinitrophenylhydrazone to have a β,γ -(LXIXb) rather than an α,β -(bridgehead) double bond (LXVIIc).



Prelog and coworkers (123, 124, 127) studied the cyclization of a series of 2-carbomethoxy-2-(3-ketobutyl)cycloalkanones (LXX) and 2-carbomethoxy-2-(3-chlorocrotyl)cycloalkanones (LXXXIII) in which the rings contained from six to fifteen carbon atoms. The products obtained were bicyclic unsaturated ketones or β -keto esters, as summarized in table 1. Cyclization of LXX through an intramolecular aldol condensation was accomplished by heating with acetic acid containing aqueous hydrochloric acid. Decarboxylation also occurred giving an α,β -unsaturated ketone, the skeleton structure of which depended upon the ring size of the starting material. With a small ring (LXX: $n = 3$ or 4) the valence-bridged-ring (fused-ring) bicyclo[$(n + 1).4.0$] structure LXXI was formed, but with a larger ring (LXX: $n = 6, 7$, or 12) the product was an atomic-bridged-ring bicyclo[$n.3.1$] derivative (LXXIIc). With a ring of intermediate size (LXX: $n = 5$) there was obtained a mixture of LXXI and LXXIIc. The double bond in LXXI and in LXXII was shown by means of ultraviolet absorption spectra to be in the bridgehead (conjugated) position.

TABLE 2

Bicyclic bridged-ring compounds obtained from nitromalonaldehyde and monocyclic ketones
(Prelog and Wiesner (128))

RING SYSTEM [n.3.1]		IMMEDIATE PRODUCT IN ALKALINE SOLUTION (SALT)	PRODUCT OBTAINED ON ACIDIFICATION
n	S*		
3	(7)		(No product isolated)
4	(8)		(No product isolated)
5	9	Colorless, LXXVb	LXXVd (keto form)
6	10	Colorless, LXXVb	LXXVe (phenol form)
7	11	Yellow, LXXVc	LXXVe (phenol form)
9-15	13-19	Yellow, LXXVc	LXXVe (phenol form)
17	21	Yellow, LXXVc	LXXVe (phenol form)
18	22	Yellow, LXXVc	LXXVe (phenol form)
27	31	Yellow, LXXVc	LXXVe (phenol form)

$$*S = [n + 3 + 1].$$

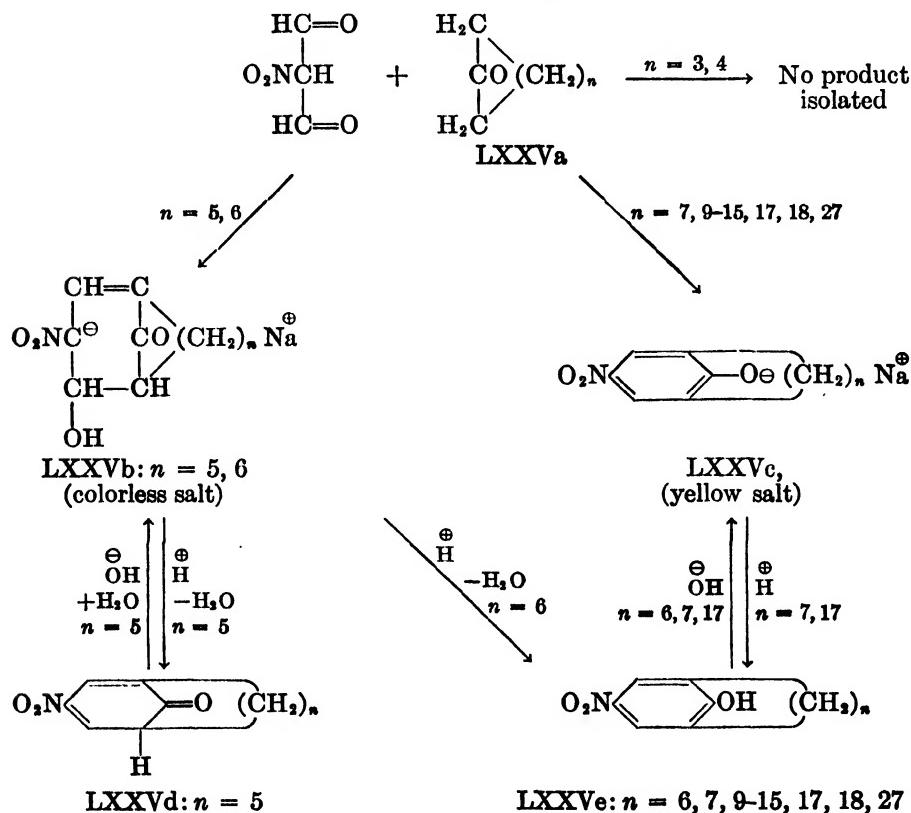
When LXXXIII was cyclized with concentrated sulfuric acid decarboxylation did not occur and, regardless of the ring size, an atomic-bridged-ring bicyclo[$n.3.1$] unsaturated β -keto ester was obtained. The position of the double bond, however, depended on the ring size of LXXXIII. With a small ring (LXXXIII: $n = 3$ or 4) the product was LXXIVa with a nonconjugated double bond, while from a larger-ring structure (LXXXIII: $n = 5$ or 10) there was obtained LXXIIa having conjugated (α,β -) unsaturation at the bridgehead. The position of the double bond in these products also was determined by study of their ultraviolet absorption spectra.

From this work it was concluded by Prelog and coworkers (123, 124, 127) that in considering stable isolable compounds Bredt's rule does not forbid a bridgehead double bond for the bicyclo[5.3.1]undecene ($S = 9$) system but that it probably does forbid a bridgehead double bond in the bicyclo[4.3.1]decene ($S = 8$) system and in bicyclo[3.3.1]nonene ($S = 7$) and its nitrogen analogs (cf. page

265). They provided an experimental verification of the viewpoint expressed earlier by Bredt (34) that with large rings the rule should not forbid a bridgehead double bond; furthermore, they determined the limiting ring size for the special case of a bridgehead double bond which is contained in the [3] branch of the bicyclo[n.3.1] system and which is also conjugated with a carbonyl group.

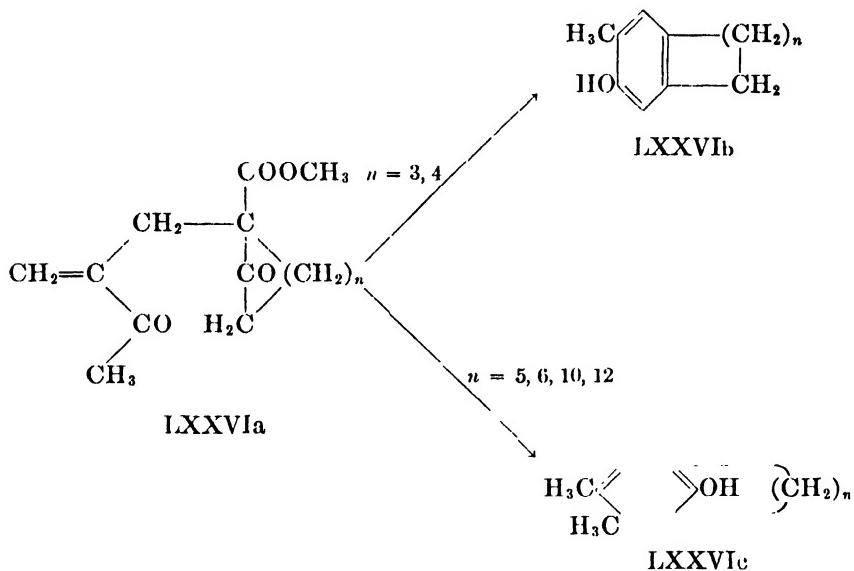
Prelog, Barman, and Zimmermann (123, 124) discussed the theoretical significance of a strained bridgehead double bond (page 227), and the decarboxylation of the bicyclic β -keto acids derived from some of these compounds was also described (cf. page 246).

Prelog and Wiesner (123, 128) investigated the formation of meta-bridged *p*-nitrophenol derivatives or related compounds by the condensation of nitromalonaldehyde with monocyclic ketones in the presence of sodium hydroxide, a method which presumably involves aldol intermediates having hydroxyl adjacent to the bridgehead. The type of product formed was found to depend upon the ring size of the ketone used. With the smaller-ring ketone (LXXVa: $n = 3$ or 4) no product was isolated. Using a larger ring (LXXVa: $n = 7, 9-15, 17, 18, 27$) the yellow *p*-nitrophenoxide salt (LXXVc) was formed directly and on acidification the meta-bridged *p*-nitrophenol LXXVe was obtained, corresponding to the behavior with open-chain analogs of LXXVa (cf. table 2).



With a ring of intermediate size (LXXVa: $n = 5$ or 6), however, only one molecule of water was eliminated in the alkaline condensation reaction and the immediate product was a colorless salt for which structure LXXVb was considered probable. Dehydration occurred on acidification of the colorless salt (LXXVb) giving with $n = 6$ the *p*-nitrophenol LXXVe, but with $n = 5$ the nonaromatic keto form LXXVd. The isolation of a compound with structure LXXVd ($n = 5$) further supports the statement of Bredt's rule to permit a bridgehead double bond in the [5] or the [3] branch of the bicyclo[5.3.1]undecene ($S = 9$) system. Evidently the coplanarity requirements for the formation of the second bridgehead double bond in the [1] branch in LXXVd \rightarrow LXXVe ($n = 5$, $S = 9$) would cause such a total strain that the ketone does not enolize even though this process would aromatize the ring.

The aromatic phenol form of this same ring size ($S = 9$) was obtained, however, in a dimethyl series starting with the condensation of monocyclic β -keto

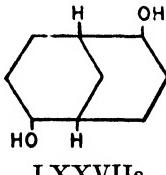


esters with the quaternary base of 1,1-bis(diethylaminomethyl)acetone. Using a large-ring β -keto ester Prelog, Wirth, and Ruzicka (130) obtained LXXVIa ($n = 10$), which on heating with acetic and hydrochloric acids gave the meta-bridged phenol LXXVIc ($n = 10$). Prelog, Barman, and Zimmermann (125) extended this work and found that from the condensation products LXXVIa, with $n = 3$ or 4, a fused-ring phenol (LXXVIb) was formed, but with LXXVIa ($n = 5$, 6, or 12) the product was the meta-bridged-ring derivative LXXVIc, as obtained in the earlier work. Thus the smallest meta-bridged benzene derivative in this series contained five members ($S = 9$), while with the 4-nitrophenols it was six members ($S = 10$). It was suggested (125) that the nonaromatic nitro derivative LXXVd is better stabilized by resonance than the analogous dimethyl compound would be, and that accordingly the increase in stability to be gained

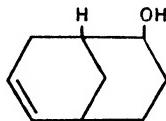
by aromatization is not as great in the nitro series as with the dimethyl compounds. The strain associated with the ring size $S = 9$ thus hinders aromatization of the nitro compound LXXVd but not of the dimethyl compound.

Evidence for the structures of these products was obtained from a study of their ultraviolet absorption spectra and their acidities. The *p*-nitrophenol derivatives were further converted to the aminophenols, to the hydroquinones, and to the quinones with meta "bridges," and the properties of these materials were also investigated (123, 128).

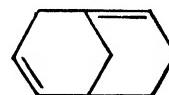
A number of investigators (e.g., 77a) have described meta- and para-bridged benzene ring compounds having large "bridges" which are presumably strainless and do not violate Bredt's rule. There apparently have been no experimental reports of the ring size required for two bridgehead double bonds which are not part of an aromatic ring (*cf.* page 226).



LXXVIIa



LXXVIIb



LXXVIIc

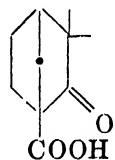
(g) Bicyclo[3.3.1]-2,6-nonanediol and bicyclo[3.3.1]-6-nonene-2-ol

It was found (106) that one molecule of water could be eliminated from the diol LXXVIIa to form an unsaturated alcohol considered to have a nonbridgehead double bond (LXXVIIb), but attempts to prepare a diene by removal of the second molecule of water were unsuccessful. Similar results were obtained on deamination of the corresponding diamine. When attempted dehydration of LXXVIIb was forced, complete resinification occurred and no bicyclo[3.3.1]-2,6-nonadiene was isolated. It was considered (106) probable that in the forced removal of the second molecule of water the steric arrangement was such as to lead not to the -2,6-diene but to the -2,5-diene (LXXVIIc) and that this intermediate, being unstable as would be expected from Bredt's rule, underwent bridge cleavage to a readily polymerized methylcyclooctatriene. Bredt at one time (34) suggested that there was a preference for the hydroxyl groups in LXXVIIa to be eliminated with the tertiary (bridgehead) hydrogens and that the first dehydration actually forms a bridgehead double bond, resulting in a moderate amount of strain. He considered this strain to be transmitted in part to the other ring, and as a consequence the second dehydration to form an additional bridgehead double bond would introduce a prohibitive amount of strain, i.e., the second elimination was hindered according to Bredt's rule. In this connection Bredt cited the observed decarboxylation of the [3.3.1] β -keto acids (page 246) as evidence for the possible existence of a bridgehead double bond in the [3.3.1] system. Bredt here evidently failed to distinguish between the steric requirements for the existence of isolable compounds and transient reaction intermediates. While there are known cases of decarboxylation of β -

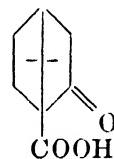
keto acids having the β -keto group in a [3] branch of the [3.3.1] system, thus indicating the possibility of a transient intermediate with a bridgehead double bond, a number of instances are known in which dehydrations in the [3.3.1] structure avoid the formation of an isolable product having a bridgehead double bond on the [3] branch (cf. page 239).

C. DECARBOXYLATION OF β -KETO ACIDS HAVING A BRIDGEHEAD CARBOXYL GROUP

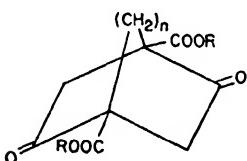
Although open-chain and monocyclic β -keto acids generally undergo decarboxylation readily, a number of bridged-ring compounds having the carboxyl group at the bridgehead position have been observed to be quite resistant to loss of carbon dioxide. It was reported by Aschan (13) that camphenonic acid (LXXVIIIa) distilled without decomposition at 310–312°C. under atmospheric pressure. Ketopinic acid (LXXVIIIb) was found (13, 88, 182) to be similarly stable toward decarboxylation, and conditions sufficiently drastic to cause loss of carbon dioxide also caused ring cleavage. Guha (70, 71) described the bicyclic diketo diacid LXXIXa as being resistant to the loss of carbon dioxide when its ester LXXIXb was heated at 200°C. for 30 min. in an autoclave with dilute



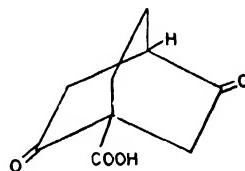
LXXVIIIa
Camphenonic acid



LXXVIIIb
Ketopinic acid



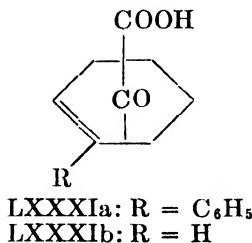
LXXIXa: $n = 2$, R = H
LXXIXb: $n = 2$, R = C_2H_5
LXXIXc: $n = 3$, R = C_2H_5



LXXX

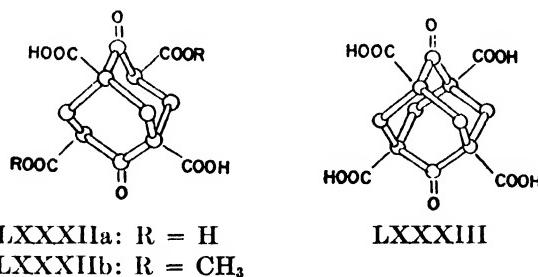
hydrochloric acid, or when subjected to other similar acidic conditions. Removal of one carboxyl group to give a low yield of LXXX, however, was reported to occur when the acid LXXIXa was heated at 270–280°C. under reduced pressure (cf. page 248). Guha also prepared the ester LXXIXc and this compound likewise resisted decarboxylation. The bicyclo[3.3.1]nonane derivative LXXXIa (49), prepared by intramolecular aldol condensation (cf. page 239), was not decarboxylated on heating in a solution of acetic acid and aqueous hydrochloric acid, nor on sublimation at 150°C. under reduced pressure. Similarly, LXXXIb (52) was not decarboxylated on heating alone or in the presence of quinoline or copper, and the corresponding saturated compound was also stable (52). The

[3.3.1] β -keto acid LXXIVb ($n = 3$; page 240) obtained by Prelog and co-workers (123, 124, 127) resisted the elimination of carbon dioxide. While the [n.3 1] derivative LXXIVb ($n = 3$) was unaffected by heating with quinoline



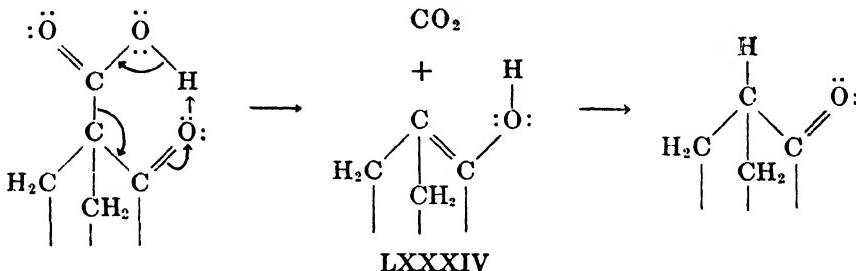
at 240°C., the higher homolog ($n = 4$) and LXXIIb ($n = 5$) (from LXXXIII) readily lost carbon dioxide under these conditions. With a still larger ring (LXXII: $n = 10$) the free acid was not isolated, since decarboxylation occurred even during alkaline hydrolysis of the ester (LXXXIIa: $n = 10$) (table 1). Decarboxylation of bicyclo[n.3.1] derivatives (LXXII: $n = 5, 6, 7$, and 12) occurred during the formation of the bicyclic system from LXX (table 1).

In contrast to the stability of the [3.3.1] acids described above, Meerwein (106) found that LXXXIIa lost all four carboxyl groups (cf. page 248), two of which are at bridgeheads, when heated with water in an autoclave at 220°C. for 1 hr. Similarly, LXXXIIb lost 2 moles of carbon dioxide from the free carboxyl groups at the bridgeheads. The tricyclic structure LXXXIII formed from LXXXII by introduction of an additional methylene bridge, however, was reported by Böttger (32) to be extremely resistant to decarboxylation.



In the decarboxylation of β -keto acids Bredt (34) suggested that the hydrogen of the carboxyl group migrates to the keto oxygen and simultaneously carbon dioxide splits out, producing the enol form of the product, which subsequently ketonizes. The stability of LXXVIIIa, LXXVIIIb, LXXIXa, and LXXXIII was interpreted by him as being due to the steric difficulty, according to the rule, of obtaining the enol form of the expected products. The work of several investigators (121, 122, 183) has shown that α,α -disubstituted β -keto acids undergo decarboxylation, that the decomposing acid absorbs 1 mole of bromine at the same rate as carbon dioxide is evolved, and that the rate of decarboxylation is essentially independent of the dielectric constant of the solvent used. These

observations have been interpreted to mean that the keto form of the keto acid can undergo the reaction, enolization of the keto acid before decarboxylation not being a prerequisite, and that the immediate product is the enol form of the ketone formed *via* a cyclic intermediate. The mechanism of the thermal decarboxylation of β -keto acids has accordingly been written (10) as follows with a quasi-ring intermediate, which is essentially Bredt's picture of the reaction in

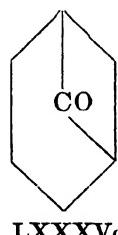
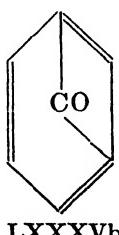
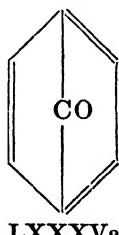


modern terms. When the α -carbon is a bridgehead in a small atomic-bridged-ring system one might expect on the basis of this mechanism and Bredt's rule that the decarboxylation will be hindered. The extent to which the reaction is hindered will, of course, be influenced by the factors which affect the strain associated with the corresponding bridgehead double bond, such as ring size and location of the β -keto group. Prelog (123) considered that the decarboxylation results can be related to Bredt's rule by assuming that in this reaction an anion at the bridgehead is an intermediate, which must be stabilized by resonance with the carbonyl group for the activation energy to be sufficiently low to permit the reaction.

In the use of Bredt's rule there may arise the problem of how "stable" a structure must be to be considered in connection with the rule. It seems likely that a bridgehead double bond might occur in a transient intermediate and yet the corresponding or analogous structure with the double bond fixed at the bridgehead may be too unstable to be isolated under ordinary conditions. Bredt considered that in the isolable anhydride of tetrahydroisophthalic acid (CIII), which has the bicyclo[3.3.1] ring system, the double bond cannot be at the bridgehead and this conclusion is supported by later work with CIII (page 256) and by results with other [3.3.1] derivatives (*cf.* page 239), yet he suggested that LXXXII can have a bridgehead double bond as required by his picture of the decarboxylation reaction. These comments imply a distinction between isolable compounds and transient reaction intermediates, although Bredt did not make use of this contrast in his discussion of the dehydration of bicyclo[3.3.1]-6-nonene-2-ol (LXXVIIb, page 244). Similarly, Prelog and coworkers found the double bond in the isolable bicyclo[4.3.1]decene derivative LXXIVb to be in the β,γ - rather than the α,β -(bridgehead) position; yet this acid undergoes decarboxylation when heated with quinoline at 240°C. If the cyclic mechanism applies to this decarboxylation, the circumstances are analogous to the [3.3.1] systems above. Conclusions about the rule in the borderline area will thus depend in part on how one interprets the qualitative word "stable."

An additional example of the inherent qualitative nature of Bredt's rule is suggested by a comparison of the decarboxylation of the bicyclo[3.3.1]- β -keto acids ($S = 7$), in which it seems that the different positions of the double bond actually correspond to different stabilities. With acids LXXXI (page 246) the enol form of the expected products would have a 1,9-double bond in the [1] branch of the [3.3.1] system, while with LXXXIIa and LXXXIIb the double bond would be in the 1,2-position and thus in one of the [3] branches; the former did not undergo decarboxylation but the latter did. From a consideration of ball-and-peg models one would expect the 1,9-double bond in the [1] branch to result in appreciably more strain than the 1,2-double bond in a [3] branch (compare page 226). If one regards the transient intermediate implied by the cyclic mechanism LXXXIV (or the resonance-stabilized bridgehead anion) to have a bridgehead double bond sufficiently tangible to be pertinent to Bredt's rule, then in borderline cases the predictions from the rule may depend on which of the bridgehead positions the double bond occupies. With the present experimental data it does not seem profitable to try to define Bredt's rule in such detail, but to consider that the rule is inherently a qualitative one. Thus there are some examples of decarboxylation for the [3.3.1] system ($S = 7$), and on this basis Bredt's rule would apply to these transient intermediates only with values of S lower than 7. If the reported conversion of the [2.2.2] acid LXXIXa ($S = 6$) to LXXX (page 245) actually occurs via the enol form, the rule would apply only with values lower than $S = 6$, although such an enol structure with $S = 6$ would be expected to have an extremely short life. Further work is needed to determine the applicability of the rule in such areas.

Zelinsky (204) attempted to prepare bicyclo[2.2.1]-7-heptanone by pyrolysis of *trans*-hexahydroterephthalic acid and its salts, but he evidently obtained little if any of the desired product (3b, 200). The ketones LXXXVa and LXXXVb, according to Stark (162), might be expected to be formed by pyrolysis of terephthalic and isophthalic acids, respectively. Stark (162) obtained a ketone by heating the calcium salt of *cis*-hexahydroisophthalic acid and assumed its structure to be LXXXVc, but Ruzicka and Trebler (140) pointed out that Stark's data are in better agreement with the properties of the unsaturated ketone 6-methyl-2-cyclohexenone (3b, 31, 110). Woodward, Brutschy, and Baer (200) commented that the conversion of dicarboxylic acids to ketones is often assumed to proceed through β -keto acid intermediates and that in the case described by Zelinsky such an intermediate would not be susceptible to decarboxylation. A β -keto acid intermediate from the hexahydroisophthalic acid similarly would be expected to resist decarboxylation.

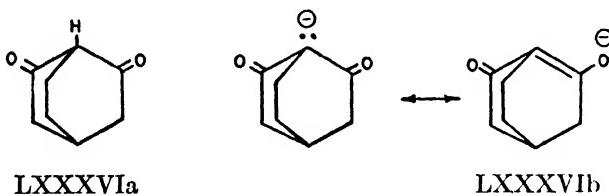


The aromatic acids do not have α -hydrogens and the formation of a β -keto acid intermediate should not be expected for this reason as well as because of Bredt's rule, and any other route leading to LXXXV_a or LXXXV_b would be hindered according to the rule.

D. ENOLIZATION AND RELATED REACTIONS OF COMPOUNDS CONTAINING ACTIVE HYDROGEN

1. Bicyclo[2.2.2]-2,6-octadione

Bicyclo[2.2.2]-2,6-octadione (LXXXVI_a) was prepared by Bartlett and Woods (24) as an example of a 1,3-diketone in which enolization involving the central hydrogen would constitute a violation of Bredt's rule. In contrast to analogous open-chain diketones LXXXVI_a gave no color with ferric chloride, gave no copper salt, showed no greater solubility in aqueous alkali than in pure water, and in a Zerewitinoff determination consumed 2 moles of Grignard reagent and evolved only 0.15 mole of gas. Bartlett and Woods explained this non-enolic character in terms of the resonance in the negative ion remaining when the proton is removed: because the central carbon is a bridgehead, a double-bonded structure such as LXXXVI_b, which would ordinarily stabilize the enolate anion of a 1,3-diketone, cannot contribute to the resonance.

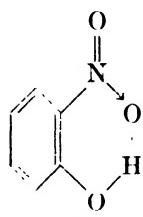


2. Monocyclic 1,3-diketones and substituted phenols

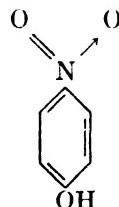
A number of differences are encountered in a comparison of the properties of certain isomeric substituted phenols, and also in a comparison of open-chain and monocyclic 1,3-diketones. These effects have been explained as being due to the steric arrangement of the groups, but Bredt's rule apparently has not been referred to in these discussions, although it provides a simple expression of the steric hindrance of chelation in many instances.

The volatility and solubility properties of some ortho-substituted phenols show characteristic differences from those of the meta and para isomers, and Sidgwick (153a) accounted for these results by considering chelation. He regarded the ortho derivative as existing in a chelate form (LXXXVII_a), where hydrogen bonding occurs intramolecularly. Sidgwick pointed out that analogous chelation cannot occur with the meta or para compounds, because an aromatic derivative cannot form a meta or para bridge (*cf.*, however, page 244), and thus with these isomers hydrogen bonding occurs intermolecularly, resulting in association. According to Bredt's rule chelate formation with LXXXVII_b to give a modified bicyclo[4.2.2] system with bridgehead double bonds would be hindered. There

are of course other factors to be considered, such as the size of the chelate ring and the possibilities for resonance.



LXXXVIIa



LXXXVIIb

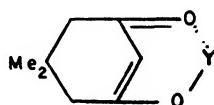


LXXXVIIIa: Y = H

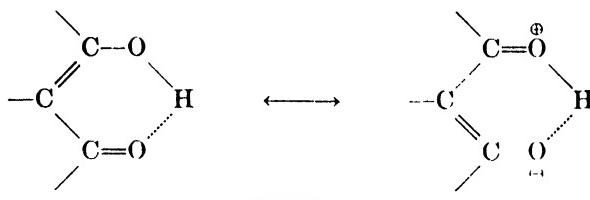
LXXXVIIIb: Y = metal, e.g., Al, Be, Cu . . . (one equivalent)

A number of properties of the enol form of an open-chain 1,3-diketone and its metal derivatives have been interpreted in terms of cyclic, resonance-stabilized chelate structures of the type of LXXXVIIIa and LXXXVIIIb. Monocyclic 1,3-diketones such as the dihydroresorcinol derivatives 1,3-cyclohexanedione and 5,5-dimethyl-1,3-cyclohexanedione (dimedon), on the other hand, have been found to differ from their open-chain counterparts in a number of instances where chelation might be expected. The contrast between the open-chain and cyclic diketones has been made in discussions of acidity (26, 148, 153b, 167, 186), of the effect of solvents on the keto-enol equilibrium (9), and of absorption spectra (28, 133), and it has been pointed out that, although enolization can occur, steric factors prevent chelation of the enol form of the cyclic 1,3-diketones. In studying the effect of structure on absorption spectra, Blout, Eager, and Silverman (28) examined dimedon and 2-ethyl-4-*n*-propyl-1,3-cyclopentanedione. These cyclic diketones showed a shift in the ultraviolet absorption maximum toward longer wave lengths on dilution, while no such change was observed with noncyclic 1,3-diketones, and this effect was attributed to ionization. They assumed that this phenomenon of increasing dissociation on dilution and the related shift in absorption spectrum is typical of all cyclic 1,3-diketones having at least one enolizable hydrogen on the carbon between the carbonyl groups. The fact that the spectrum of open-chain diketones did not depend on concentration was considered to be due to the occurrence of intramolecular hydrogen bonding, which is not possible with the cyclic derivatives because of the fixed spatial arrangement of the carbon-carbon bonds. Rasmussen, Tunnicliff, and Brattain (133) accounted for the spectra of enolized 1,3-diketones by the resonance-stabilized chelate form LXXXVIIIId, referred to as "conjugated chelation" to differentiate it from ordinary intramolecular hydrogen bonding. They considered

the spectrum of dimedon, which indicated this "conjugated chelation" type of enolization, to illustrate a type of structure in which resonance stabilization of the ionic structure can be realized by dimerization (LXXXVIIIe), since the ring makes it impossible sterically for the hydroxyl group of the enolized form to approach closely enough to the carbonyl oxygen of the same molecule to interact with it in the manner shown in formula LXXXVIIId. These steric effects can be

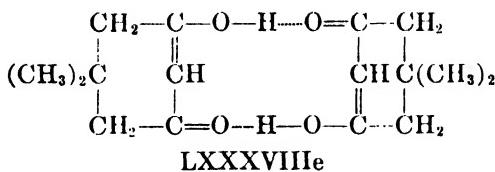


LXXXVIIc: Y = H or metal



LXXXVIIId

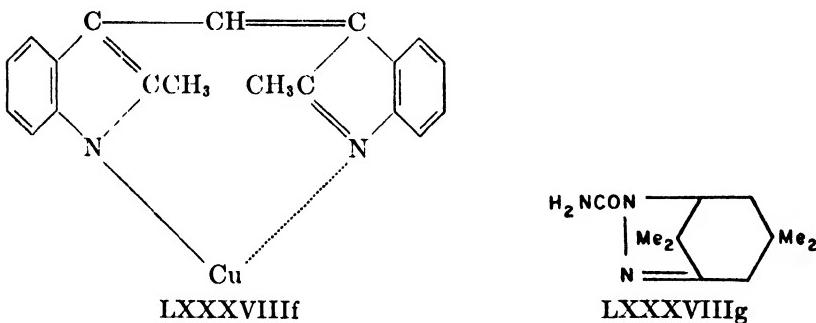
described as instances in which, according to Bredt's rule, chelation of the enol form of the cyclic diketones is not possible unless the ring size of the diketone is large, since the bridged-ring chelate structure LXXXVIIc has bridgehead double bonds. Thus the shift in absorption spectrum on dilution may not be characteristic of large-ring cyclic β -diketones where Bredt's rule allows a bridgehead double bond.



Weygand and Forkel (185) prepared beryllium and aluminum salts of 5,5-dimethyl-1,3-cyclohexanedione (dimedon) by exchange with the corresponding metal derivatives of ethyl acetoacetate. They found the properties of these cyclic β -diketone derivatives to be entirely different from those of the open-chain β -diketones. These salts melted with complete decomposition at temperatures near 300°C., they could not be distilled in high vacuum but rather decomposed, and they were not soluble in inert solvents such as benzene and chloroform. Solution occurred transitorily in methanol or ethanol but solvolysis took place to regenerate dimedon. They dissolved in ethyl acetoacetate but in doing so gave the chelate derivative of the ester and free dimedon. Molecular weight determinations could not be made, owing to insolubility in suitable solvents. Weygand and

Forkel pointed out the necessity for spatial proximity of the two oxygen atoms in order to obtain the typical chelate derivatives LXXXVIIIb, and they attributed the difference in behavior of the open-chain and the dimedon metal derivatives to the fixation of the two carbonyl groups in the cyclohexane ring. According to Bredt's rule, one would expect that normal chelate metal derivatives could not be obtained from monocyclic 1,3-diketones, except those having large rings, because these derivatives (LXXXVIIIc) would be bridged-ring structures with bridgehead double bonds. Similarly, the proposed chelate structure LXXXVIIIf (56) seems inconsistent with Bredt's rule.

Methylation of dimedon gave a mixture containing 2,2,5,5-tetramethyl-1,3-cyclohexanedione, whose disemicarbazone was reported by Hirsjärvi (75) to be converted on heating to the pyrazoline derivative LXXXVIIg. The product was a high-melting (325°C.), highly insoluble material which could not be purified, and its structure was not proved. While open-chain 1,3-diketones form heterocyclic derivatives by reaction with amidines (forming pyrimidines), with hydrazine or its derivatives (forming pyrazoles), or with hydroxylamine (forming isoxazoles, from monooximes), the formation of analogous heterocyclic compounds (including LXXXVIIg) from monocyclic 1,3-diketones with relatively small rings would be hindered, according to Bredt's rule, since the expected bridged-ring products would have bridgehead double bonds. It has been pointed out (145) that dioximes can be obtained from monocyclic 1,3-diketones but not from the open-chain type, since with the latter the formation of isoxazoles is preferred.

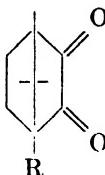


3. Camphorquinone and camphenilone

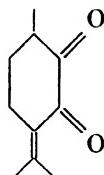
When camphorquinone (LXXXIXa) was treated with sulfuric acid an isomeric product was obtained which Manasse and Samuel (103) considered to have the enolic structure LXXXIXc. Bredt, Rochussen, and Monheim (42), at a time before Bredt's rule had been described, regarded this structure as unlikely in view of an analogous instance in which camphor underwent bridge cleavage. This reinvestigation showed that the product obtained was the monocyclic compound XC. This reaction was cited by Bredt (44) in support of the rule.

Bredt and Doerenkamp (37) attempted the bromination of camphorquinone to obtain LXXXIXb, by analogy with the bromination of camphor, but they were not successful. Likewise, Bredt-Savelsberg (45) was unable to obtain XClb

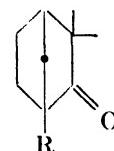
by the bromination of camphenilone (XCIIa). Considering the bromination of ketones to occur by the addition of bromine to the enol form, Bredt (44) accounted for the failure of these brominations to occur because, according to the rule, these ketones cannot enolize.



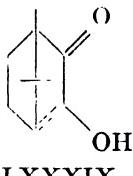
LXXXIXa: R = H
LXXXIXb: R = Br



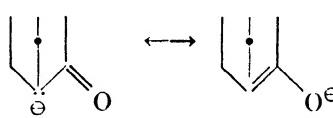
XC



XCIIa: R = H
XCIIb: R = Br
XCIIc: R = CH₃



LXXXIXc



XCII

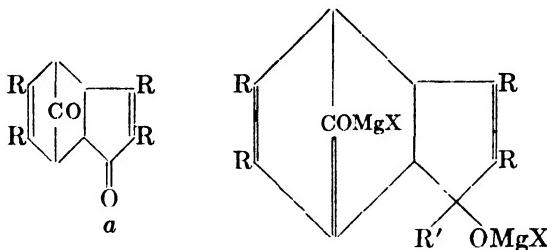
Ruzicka (136) indicated that a hypothetical synthesis of fenchone (XCIIc) by Haller-Bauer methylation of camphenilone (XCIIa) at the bridgehead position is not operable, since at ordinary temperatures XCIIa on steric grounds would not react with sodium amide to form the enolate anion, while at higher temperatures it has been found by Semmler (149) that cleavage occurs to form (after hydrolysis) 3-isopropylcyclopentanecarboxamide. The steric reason for the failure of XCIIa to form the enolate anion might be described in the same way as Bartlett and Woods (24) explained the non-enolic character of bicyclo[2.2.2]2,6-octadione (LXXXVIIa) (page 249). That is, resonance stabilization as shown in formula XCII is inhibited according to Bredt's rule. Similarly Allen, Jones, and Van Allan (5) found that camphorquinone (LXXXIXa) in the Zerewitinoff analysis showed two additions with methylmagnesium iodide but no evolution of methane (active hydrogen).

The failure of these compounds to enolize was further shown by their non-exchange with deuterium. Nesmeyanov and coworkers (113) reported that the α -hydrogens of camphorquinone and camphenilone failed to exchange with deuterium when these compounds were heated in an autoclave with dioxane-heavy water containing potassium hydroxide for 70 hr. at 130–135°C., while simpler ketones readily underwent the exchange. They considered the nonexchange to be due to the failure of these bridged-ring ketones to enolize, according to Bredt's rule.

4. Substituted bicyclo[2.2.1]-2-hepten-7-one system

Allen and coworkers (3, 4) found that XCIII reacted with 2 moles of Grignard reagent in the Zerewitinoff determination, showing one addition and one active hydrogen. They attributed this result to addition at carbonyl α and enolization

at the carbonyl bridge as shown in XCIV. This structure was assumed because hydrolysis of the addition complex regenerated a monocarbinol which showed thermal decarbonylation, a reaction which they had found characteristic of

XCIII: $R = C_6H_5$ XCIV: $R = C_6H_5$; $R' = CH_3$

carbonyl bridge compounds having the bicyclo[2.2.1]-2-hepten-7-one structure. In later work (7), however, they found this assumption involving a supposed exception to Bredt's rule to be no longer tenable. They examined the analogous compound camphorquinone, suggested by Woodward, and found that it showed addition but no enolization with the Grignard reagent (*cf.* page 253). The structure then favored for the magnesium enolate was one in which one of the rings was opened.

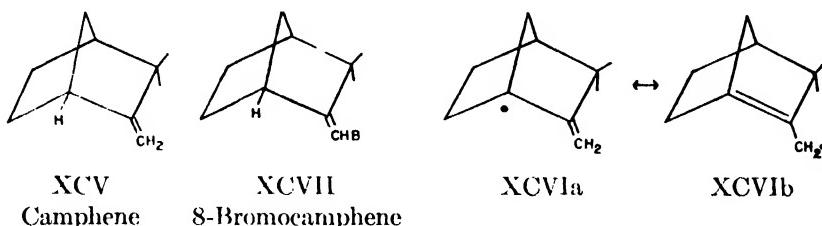
5. Triptycene

The activity of the "methyl" hydrogen in triptycene (XIXb) and in triphenylmethane parallels the reactivity of the corresponding halogen compounds, the bridged-ring structures being considerably less active. Bartlett, Ryan, and Cohen (23) found that triptycene gave no exchange with phenyllisopropylpotassium under conditions which lead to immediate reaction in the case of triphenylmethane; that triptycene was not chlorinated by sulfonyl chloride in the presence of benzoyl peroxide, whereas toluene under identical conditions gave a high yield of benzyl chloride; and that chromic anhydride under conditions which lead to the formation of triphenylmethylcarbinol from triphenylmethane formed only anthraquinone and carbon dioxide from triptycene. They considered that to the extent that the central hydrogen in triphenylmethane is activated by the possibility of resonance in the triphenylmethide ion, such activity should be diminished or absent in triptycene. Forms such as XXI (page 230) should be unimportant, according to Bredt's rule, in stabilizing the anion, cation, or free radical from triptycene.

6. Camphene

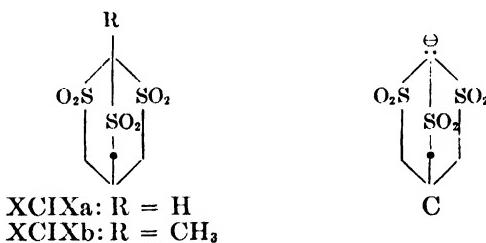
In examining the scope of *N*-bromosuccinimide as a brominating reagent for allylic positions Roberts and Trumbull (134) investigated its reaction with camphene (XCV) in which the only allylic hydrogen is at a bridgehead. They pointed out that form XCVIb would not be expected to contribute to the resonance stabilization of the free-radical intermediate XCVIa, and that if such resonance stabilization is necessary the allylic bromination of camphene with

this reagent should be difficult or impossible. The product obtained from *N*-bromosuccinimide and camphene was a mixture of bromides of which the principal (65 per cent) component was 8-bromocamphene (XCVII) and there was no indication of the presence of the bridgehead halide. Bromination of bicyclo[2.2.1]-2-heptene (norbornylene) similarly did not give the bridgehead (allylic) derivative (135). Roberts and Trumbull pointed out the failure to accomplish related reactions with triptycene (*cf.* page 254).



7. Bicyclic trisulfone

Doering and Levy (59) prepared the bicyclic trisulfone XCIXa in an investigation of the acidity of hydrogen alpha to the sulfone group. This compound was found to dissolve in aqueous sodium bicarbonate without decomposition, while its 1-methyl homolog (XCIXb) was insoluble even in sodium hydroxide solution. A close comparison with the work of Bartlett and Woods (24) on bicyclo[2.2.2]-2,6-heptadione (page 249), however, was not possible. They considered that the



stabilization of the negative charge in the anion C by the inductive effect of the adjacent groups would be unaffected by the steric configuration of the trisulfone. On the other hand, resonance involving orbitals of the sulfur might not be inhibited if such hybridization allows the use of octahedral bond angles. Thus Doering and Levy suggested that Bredt's rule may not apply to C=S, but since the question of the occurrence of an actual carbon-sulfur bond is unsettled, it is not certain how Bredt's rule applies in this instance (2a, 72c).

E. ANHYDRIDE FORMATION

1. Dehydrocamphoric acid

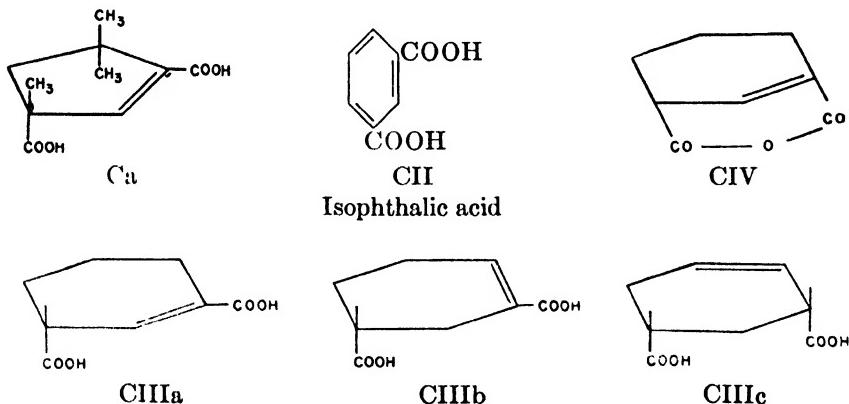
The failure of dehydrocamphoric acid (III) to form its anhydride and the rearrangement of the double bond to the position as in VI on forced dehydration have been discussed (page 220).

2. Dehydroisofenchocamphoric acid

Toivonen (174) found that when dehydroisofenchocamphoric acid (Ca) was heated alone or was heated with acetyl chloride at 150°C. no monomeric anhydride could be obtained. He attributed this result to steric hindrance of the kind which prevents the formation of the anhydride of dehydrocamphoric acid (page 221). Using Bredt's terminology he described the carboxyl groups as being in the *meso-trans* position to one another as a consequence of the double bond and thus unable to come close enough together to form the anhydride. Bredt (44) cited this work in support of the rule. In this structure there is no other position available for the migration of the double bond to permit a reaction analogous to the one which occurs with dehydrocamphoric acid (III).

3. Isophthalic acid and its hydro derivatives

In discussing the anhydride formation of dehydrocamphoric acid Bredt, Houben, and Levy cited isophthalic acid (CII), which does not form an anhydride, and hexahydroisophthalic acid (presumably the *cis* form), which readily gives one. Perkin and Pickles (119, 120) had reported that of the three position isomers of tetrahydroisophthalic acid, only CIIIa forms an anhydride and that CIIIb and CIIIc when treated with acetic anhydride give the same anhydride as CIIIa by a rearrangement of the double bond. Bredt (35) objected to this conclusion, since

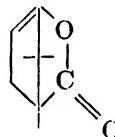
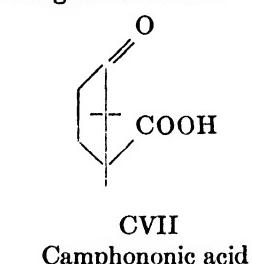
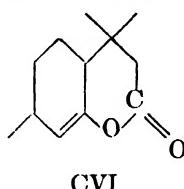
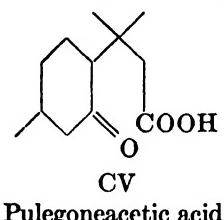


in the derivative of CIIIa, i.e., CIV, a double bond occurs at the bridgehead of a small atomic-bridged-ring system. Bredt compared the steric situation in structure CIV with the simpler hypothetical monocyclic anhydride of the fumaric acid-like forms of methylglutaconic acid and concluded that CIIIa could not form an internal anhydride. Further investigation by Farmer and Richardson (61, 62), who did not refer to Bredt's paper (35) or to Bredt's rule, showed that the anhydride-forming isomer supposed by Perkin and Pickles to be the Δ^1 acid (CIIIa) is actually the *cis* Δ^4 acid (CIIIc), a result which is consistent with Bredt's rule. Bredt (35) proposed the generalization that an eight-membered oxygen-containing ring with a one-membered bridge in the 1,5-position, i.e.,

a [3.3.1] system, cannot be formed when a double bond occurs at a bridgehead (*cf.*, however, page 244).

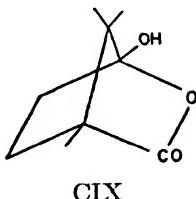
F. ENOL LACTONIZATION OF γ - AND δ -KETO ACIDS

Vorländer (176) reported that the monocyclic compound pulegoneacetic acid (CV) when heated at 115°C. slowly loses water to form the bicyclic valence-bridged-ring enol lactone CVI (or isomer with double bond common to both rings). With camphononic acid (CVII), however, an analogous reaction would lead to CVIII with a double bond at a bridgehead in a small atomic-bridged-ring structure. CVII, m.p. 228°C., was found to sublime or distill in the temperature range 260–290°C. without dehydration or other decomposition. Windaus and Bohne (193) described the hindrance of the reaction leading to this enol lactone by applying Bredt's rule to the expected product. Bredt's rule was also used by



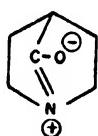
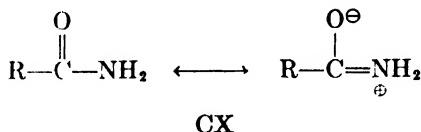
Windaus and Bohne in interpreting the behavior of some keto acids obtained in the degradation of steroids. Although later work has revised some of these structures, they made a reasonable generalization based on Bredt's rule that enol lactones would not be obtained from the cyclohexanonecarboxylic acids, and that with cyclohexanoneacetic acids such products would be formed only from the "ortho" or 2-acetic acid derivatives.

If the mechanism of enol lactone formation involves the dehydration of a lactol intermediate (152) such as CIX, then the dehydration step is evidently the hindered process (*cf.* Section B,1, page 235).

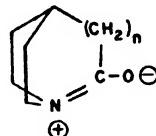


G. FORMATION AND REACTIONS OF LACTAMS

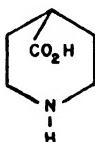
Considering the double-bond character (CX) of the C—N bond in amides, Lukeš (102) applied Bredt's rule to the bicyclic structures CXI, CXIIa, and CXIIb, which he concluded, according to the rule, probably cannot be formed.



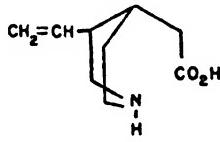
CXI

CXIIa: $n = 1$ CXIIb: $n = 2$

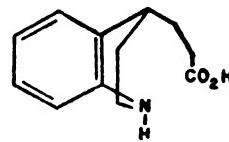
In this way he accounted for the failure of CXIII to lactamize even when heated above 300°C. The similar behavior of meroquinene (CXIV), m.p. 236°C., which underwent decomposition without giving the bicyclo[2.2.2]lactam, and of CXV, which did not cyclize, were also interpreted in this way. Lukeš pointed out that these compounds which he described as sterically "impossible," might be prepared some time by another procedure but if they were made they would have an actual carbonyl group with properties different from those which we recognize as characteristic of amides.



CXIII



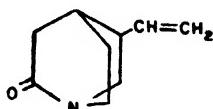
CXIV



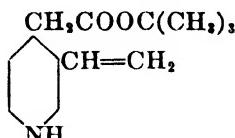
CXV

Meroquinene

In studying the autoxidation of quinonone with oxygen in the presence of potassium *tert*-butoxide Doering and Chanley (58) attempted to isolate an intermediate cleavage fragment CXVI, but only the product (CXVII) of further cleavage was found. They too considered the unknown type of bicyclic amide



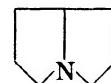
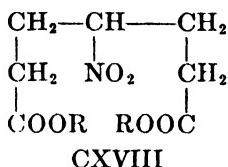
CXVI



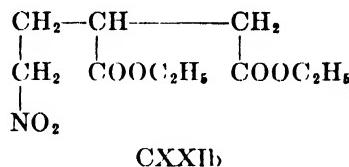
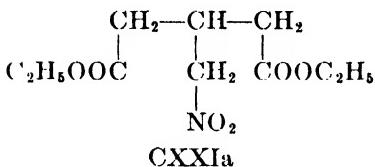
CXVII

with nitrogen as the bridgehead to be more reactive than ordinary amides and quoted Woodward's interpretation of this reactivity: "The atoms attached to the carbon of the carbonyl and to the nitrogen atom at the bridgehead cannot attain coplanarity and consequently normal amide resonance, which involves some double bond character for the C—N link, will be inhibited. Accordingly amides of this type would be expected to exhibit the reactive properties of a more or less isolated carbonyl group."⁴

Leonard and coworkers (93, 94) developed a method for the preparation of pyrrolizidines (CXIX) from γ -nitropimelic esters (CXVIII) by two-step catalytic hydrogenation, first with platinum oxide at low pressure and then with copper chromite at high temperature and pressure. They considered that, following the



CXIX



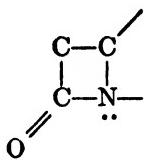
CXX

reduction of the nitro group, bicyclic amide intermediates were formed which were then further reduced to the bicyclic amine. Attempts by Leonard and Shoemaker (95) to prepare the atomic-bridged-ring amine CXX by reduction of CXXIa or CXXIb, however, were not successful. While the amide intermediates in the preparation of pyrrolizidines are valence-bridged-ring compounds, the analogous ones from CXXIa or CXXIb would have atomic-bridged-rings with nitrogen as the bridgehead like the structures discussed above. Thus the failure to obtain CXX may have been due in part to the hindrance according to Breit's rule of reactions leading to the atomic-bridged-ring amide intermediates.

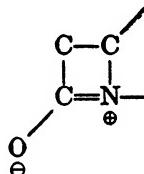
Woodward (202) pointed out that the amide link in β -lactams, and particularly in penicillin, should not be normal. With simple β -lactams the ratio of the contributions of the two forms CXXIIa and CXXIIb will differ from that with normal

⁴ Albertson (1a) has recently reported the synthesis of the bicyclic amide 5-carbethoxy-9-methyl-2-oxo-1-azabicyclo[3.3.1]nonane. It would seem that normal amide resonance in this [3.3.1] system would be somewhat hindered, with a consequent decrease in stability as compared with ordinary amides.

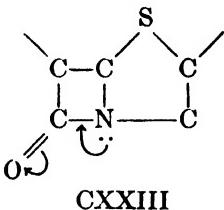
amides, the latter contributing less since the introduction of the double bond into the cyclobutane ring will be somewhat opposed by strain set up as a consequence of angular distortions. In penicillin Woodward considered that this effect



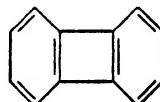
CXXIIa



CXXIIb



CXXIII

CXXIV
Biphenylene

should be considerably magnified, since here the normal displacement shown in the partial structure CXXIII confers partial double-bond character on a link at the "bridgehead" of a small nonplanar bicyclic system. This effect was explained alternatively by applying Bredt's rule, according to which the resonance stabilization described above would be damped. Like biphenylene (CXXIV) (14), CXXIII is a valence-bridged-ring (fused-ring) structure rather than an atomic-bridged-ring one, and although these compounds are clearly strained they are regarded as outside the scope of Bredt's rule (page 222).

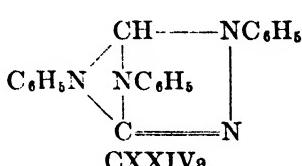
H. MISCELLANEOUS STRUCTURES

In addition to the examples described above other structures have appeared in the literature which are pertinent to Bredt's rule. No attempt has been made to obtain a complete list, but the following additional ones are included here.

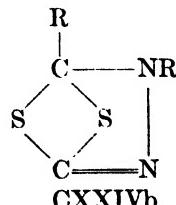
1. Bicyclic systems

(a) [2.1.1] Ring system: nitron

Wittig (197b) considered it surprising, in view of Bredt's rule, that nitron was regarded as having structure CXXIVa. Schönberg (146) reemphasized the stereochemical difficulty according to this rule of forming structures like CXXIVa

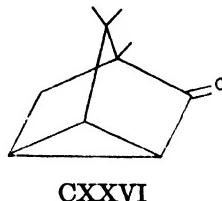
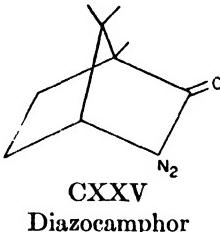
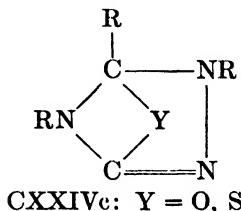


CXXIVa



CXXIVb

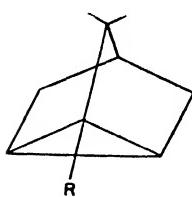
and proposed an alternative structure for nitron. He also called attention to the fact that the generally accepted structures CXXIVb and CXXIVc for several heterocyclic compounds do not conform to Bredt's rule and suggested other structures for compounds of this kind. Sidgwick (154) referred to CXXIVa as sterically improbable.



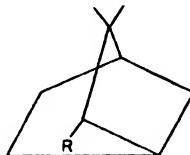
(b) [2.2.1] Ring system

(1) *Diazocamphor*.—Angeli (8) reported the product obtained on thermal decomposition of diazocamphor (CXXV) to be the unsaturated bicyclic ketone XXIV (page 231). Bredt and Holz (38) considered this structure improbable according to Bredt's rule, and their reinvestigation showed that the material was actually a saturated tricyclic ketone (CXXVI), a derivative of cyclene. 2-Diazocamphane was reported by Heubaum and Noyes (73) to give a similar cyclization product (cyclene), and Wilson (191) found that dehydrobromination of bromoisocamphenilanic acid (structure LII, page 237, with Br replacing OH) with aqueous sodium carbonate gave tricyclene acid rather than an unsaturated acid as had been previously reported.

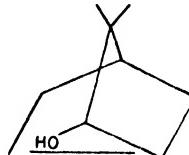
(2) *Apotricyclenol*.—Lipp and Padberg (99) considered that the tertiary alcohol apotricyclenol (CXXVIIa), an analog of cyclopropanol, should readily undergo ring-cleavage and rearrangement reactions, but that formation of CXXVIIId by a reaction analogous to the observed conversion of cyclopropylamine to allyl alcohol would be prevented, according to Bredt's rule. When CXXVIIa was heated alone or with hydrochloric acid, camphenilone (CXXVIIIa) was obtained, the reaction resembling the reported transformation of ω -aminotricyclene hydrochloride (CXXVIIb) to camphenilanaldehyde (CXXVIIIb) and of tricyclene (CXXVIIc) to camphene (CXXVIIIc) via camphene hydrochloride.



CXXVIIa: $\text{R} = \text{OH}$
 CXXVIIb: $\text{R} = \text{CH}_2\text{NH}_2 \cdot \text{HCl}$
 CXXVIIc: $\text{R} = \text{CH}_3$



CXXVIIIa: $\text{R} = \text{---O}$
 CXXVIIIb: $\text{R} = \left\{ \begin{matrix} \text{CHO} \\ \text{H} \end{matrix} \right.$
 CXXVIIIc: $\text{R} = \text{---CH}_2$

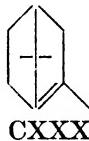


CXXVIIId

(3) *Others.*—Bredt, Thouet, and Schmitz (44) considered structures CXXIX and CXXX, which Bartelt proposed for fenchene, to be improbable. γ -Pinene was believed by Wallach and Blumann (179) to be CXXXI, but it has been pointed out (168a) that this structure is sterically impossible, according to



CXXIX

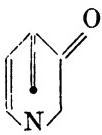


CXXX

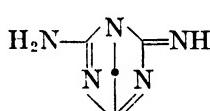
Bredt's rule. Ochiai and Ikuma (108, 114) tentatively suggested CXXXIIa as one possible structure for a product obtained in the Houben-Hoesch self-condensation of *N*-cyanomethylpyrrole. The molecular weight of the material, m.p. 307–308°C., could not be determined because of insolubility, however, and proof of structure was not undertaken.



CXXXI

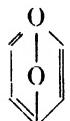


CXXXIIa



CXXXIIb

Slotta and Tschesche (156) assumed structure CXXXIIb for a compound formed by the reaction of ethyl chloroacetate and biguanide. Structures suggested for γ -pyrones (CXXXIIc) (15, 48) and for *N*-substituted γ -pyridones (CXXXIId) (159), in addition to their valence difficulties, are not consistent with Bredt's rule.



CXXXIIc

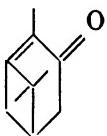


CXXXIId

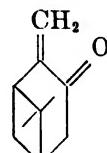
(c) [3.1.1] Ring system: carvopinone

A product designated carvopinone was obtained by Wallach and Engelbrecht (180) on heating nitrosopinene with aqueous oxalic acid. The material was unstable and was not obtained in a pure state, since it was found to be readily converted to the monocyclic compound carvone (2-methyl-5-isopropenyl-2-cyclohexenone). They considered (180, 181) carvopinone to be CXXXIV, being derived from nitrosopinene which they thought to have the older structure XXXV (page 233). Ruzicka and Trebler (141), however, showed the structure of nitrosopinene to be XXXVII (cf. page 233). Structure CXXXIV for carvopinone was evidently accepted even quite recently (3, 68, 82, 137, 140, 155c, 160, 161), although it is in disagreement with Bredt's rule. Schmidt (81e, 143, 144, 155c) recently reported that the product commonly called carvopinone is really

pinocarvone, having structure CXXXV, and that the material commonly described as pinocarvone is actually the aldehyde myrtenal. He suggested that the



CXXXIV

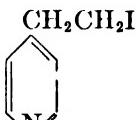


CXXXV

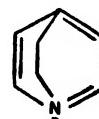
name carvopinone and the structure CXXXIV be disregarded.

(d) [2.2.2] Ring system

Löffler and Stietzel (101) investigated the synthesis of bicyclic amines by reduction and intramolecular alkylation of 2-(δ -iodobutyl)pyridine and 4-(β -iodoethyl)pyridine (CXXXVI). While 2-(δ -iodobutyl)pyridine gave the bicyclic valence-bridged-ring derivative, unsatisfactory results were obtained in making quinuclidine from CXXXVI. The pyridinium salt of CXXXVI was written as



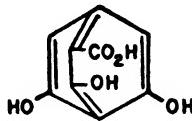
CXXXVI



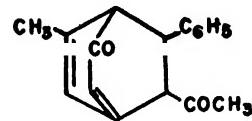
CXXXVII

CXXXVII, although no conclusive evidence for this monomeric structure was obtained. This representation was later shown (107) to be incorrect, since the product obtained was polymeric, a result of intermolecular rather than intramolecular salt formation.

Leuchs and Simion (96) reported structures CXXXVIII and CXXXIX for by-products obtained in the preparation of phloroglucinol derivatives.

CXXXVIII: R = COOC₂H₅
R' = OCOCH₃

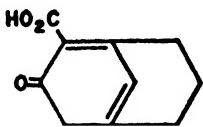
CXXXIX



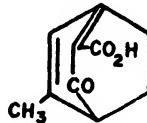
CXL

The condensation of benzaldehyde with 2 moles of acetylacetone followed by removal of 2 moles of water with ethanolic hydrochloric acid yielded a diketone, and CXL was considered (86) as one of three possible structures for this product. Knoevenagel and Mottek (87) regarded CXLIa or CXLIb as a possible structure for the cyclization product of ethyl 3-methyl-2-cyclohexenylidenecyanoacetate. Mohr (110) pointed out that these structures are contrary to Bredt's rule and are therefore open to question. Structure CXLIc considered (86) for the dioxime

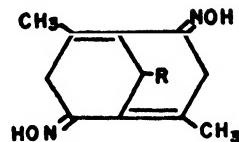
formed from 4,6-diacetyl-3-methyl-5-phenyl-2-cyclohexenone and hydroxylamine also is inconsistent with Bredt's rule.



CXLIa

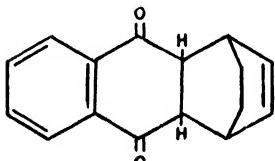


CXLIB

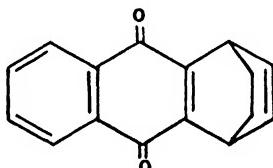


CXLIc: R = C6H5

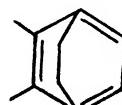
On mild dehydrogenation CXLIB was found to lose only two hydrogens to form CXLIc. Diels and Alder (57) considered this reaction to show that Bredt's rule is valid for a two-membered bridge as well as for the one-membered bridge in the pinane and camphane series, since aromatization would lead to the improbable structure shown partially in CXLIV. Aromatization does occur on heating CXLIc, but the bridge is eliminated in the process.



CXLIID



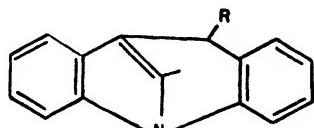
CXLIID



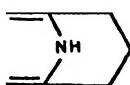
CXLIV

(e) [3.2.1] Ring system

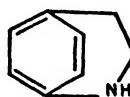
Structures CXLV, where R is a keto or a bis(β -indolyl)methyl radical (172, 173), are inconsistent with Bredt's rule. The diethyl ester of N-methyl-2,5-pyrrolidinediacetic acid was found to undergo a Dieckmann condensation to a tropane derivative but the corresponding pyrrole derivative did not. Willstätter and Bommer (189) called attention to the fact that this reaction is hindered for spatial reasons, since the expected product (CXLVI) would be extraordinarily strained because of the distortion of valence bonds. By comparison, they considered that benzene cannot have a meta or para bridge containing two or three carbon atoms, and accordingly the identity of Braun's reported "dihydro-*p*-indol" (CXLVII) was questioned.



CXLV



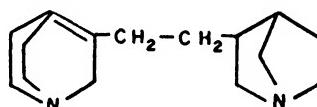
CXLVI



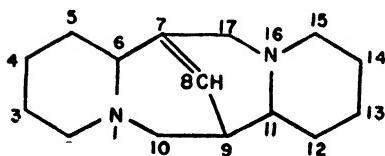
CXLVII

(f) [3.3.1] Ring system

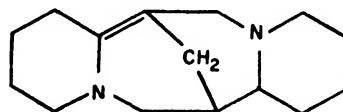
(1) *Spartein derivatives.*—Two different isomeric bases, $C_{18}H_{24}N_2$, derived from spartein, $C_{16}H_{24}N_2$, have been reported, one by Willstätter and Marx (190), designated spartyrin, and the other by Wolffenstein and Reitman (198), named dehydrospartein. Wolffenstein and Reitman suggested structure CXLVIII for dehydrospartein, based on the currently used structure of spartein, but Schöpf and Braun (147) objected to this in view of Bredt's rule. Winterfeld and Schirm



CXLVIII



CXLIX

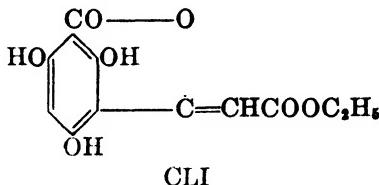


CL

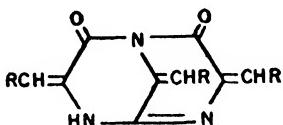
(196) reviewed the above work, including that of Schöpf and Braun, and from their oxidative degradation studies, together with the structure since suggested for spartein, proposed structure CXLIX for dehydrospartein and CL for Willstätter and Marx's isomeric spartyrin. Prelog, Ruzicka, Barman, and Frenkiel (127) considered it improbable that Bredt's rule should not apply to these nitrogen analogs of bicyclo[3.3.1]nonane written by Winterfeld and Schirm. In a later paper, however, Winterfeld and Besendorf (194) accepted the position of the double bond in the [1] branch of the [3.3.1] system (CXLIX) as unlikely in view of Bredt's rule, as Prelog had pointed out (194), but they did not refer to CL, in which the double bond is in one of the [3] branches. Winterfeld and Rönsberg (195) had considered structures for didehydrospartein having double bonds in (a) the 4,5- and 11,12-positions and (b) the 4,5- and 9,11-positions, but Winterfeld and Besendorf (194) indicated that both of these structures agree with Bredt's rule. The rule, however, is regarded as prohibiting any bridgehead double bond in the central [3.3.1] system, i.e., in the 6,7-, the 7,8-, or the 7,17 position (CXLIX) or the other corresponding locations. Beyler (27) has apparently reexamined the structures of these unsaturated bases.

(2) *Others.*—Jerdan (80) wrote the meta-bridged phloroglucinol structure CLI for the product obtained by the reaction of sodium with acetonedicarboxylic ester. In view of its strong acidity Leuchs and Sperling (97, 159) suggested, however, that the product obtained was actually a hydroxycoumarin derivative, although no reference was made to Bredt's rule. On treating the azlactone of acetyldehydrophenylalanyldehydrophenylalanyldehydrophenylalanine with so-

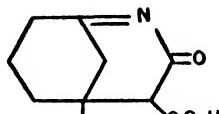
dium hydroxide, Tietzman, Doherty, and Bergmann (170) obtained a product, having the composition $C_{21}H_{19}O_2N_3$, for which structure CLII appeared more probable to them than two isomeric bicyclic systems. The latter were also bridged-ring structures with bridgehead double bonds. When ethyl (1-methyl-3-



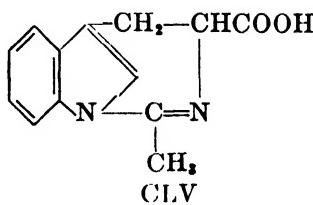
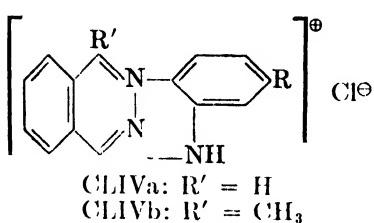
ketocyclohexyl)cyanacetate was heated with 15 per cent hydrochloric acid, an acidic compound was formed to which Farmer and Ross (63) assigned structure CLIII. Barltrop (16) observed that this structure is improbable for several



CLII: R = C_6H_5



CLIII

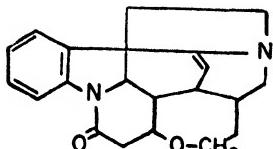


reasons, including the fact that it violates Bredt's rule. Vaughan (175) pointed out that structures CLIVa and CLIVb, which had been proposed by other workers, embody flagrant contradictions of Bredt's rule.

(g) [4.2.1] Ring system

A compound formed from acetyl chloride and tryptophan was believed by Wrede and Feverriegel (203) to be CLV.

2. Complex ring systems



CLVI



CLVII



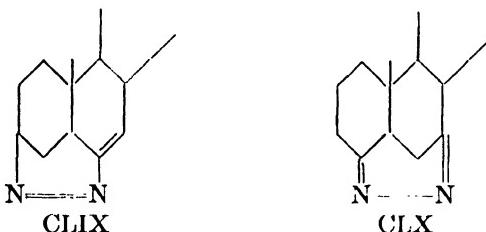
CLVIII

(a) Strychnine and neostrychnine

In discussing the structure of strychnine, Woodward (199) regarded structure CLVI as sterically impossible. Prelog and Häfliger (126) used Bredt's rule to account for the low basicity of neostrychnine (shown partially in CLVII), in which the double bond is in the α,β -position to the nitrogen. Adams and Mahan (1) reported that vinyl tertiary amines in general exhibit stronger basicities than the corresponding saturated compounds, and they explained this by assuming conversion to the quaternary ammonium hydroxide. Prelog and Häfliger considered that the low basicity of neostrychnine (*cf.* CLVII) is due to the steric hindrance, according to Bredt's rule, of the formation of the quaternary ion shown partially in CLVIII.

(b) Steroid diketone derivatives

A procedure commonly used in characterizing steroid 1,4-diketones is their reaction with hydrazine. The resulting products have usually been regarded (65, 165, 192) as pyridazine derivatives, by analogy with the behavior of open-chain 1,4-diketones. Fernholz (65) concluded from steric considerations that the double bonds must be in the positions shown in the partial structure CLIX, and he pointed out that structures with the double bonds in other positions could not be constructed with models. Double bonds in the positions shown in CLX (115) would presumably involve considerable strain.

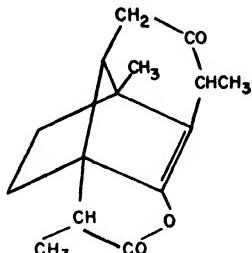


In some instances it has been reported (103a, 113a, 165) that the derivatives obtained are actually polymeric, and therefore that the formation of a "product" from hydrazine and the diketone does not constitute proof of the 1,4-positions of the carbonyl groups. Similarly, Windaus (192) found that cholestane-^{1,4}dione and ammonia gave a product which appeared to result from a dehydration reaction involving 2 moles of the diketone and 1 mole of ammonia, rather than a pyrrole derivative as is formed with open-chain 1,4-diketones. If one regards CLIX and CLX as modified bicyclo[6.2.2] systems, the double-bond arrangement CLIX preferred by Fernholz contains one bridgehead double bond in the [6] branch, while the alternative structure CLX has two bridgehead double bonds in one of the [2] branches. Models indicate CLX to have considerable strain, in contrast to CLIX.

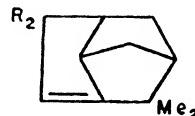
(c) Others

Woodward and Kovach (201) considered the enol-lactone structure CLXI for the santonides incorrect, since it possesses a carbon-carbon double bond in

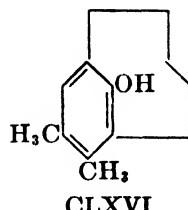
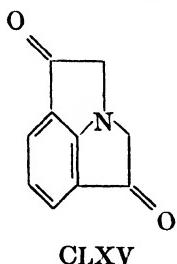
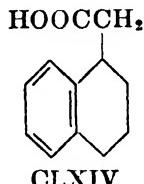
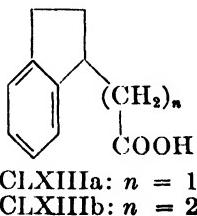
an impossibly strained position at the bridgehead in a bicyclo[3.2.1]octane ring system. Their further investigation of these products supported a different enol-lactone structure in which such strain is not present.



CLXI

CLXII: $R = C_6H_5$

Lipp and Quaedvlieg (100) treated ω -benzoylcamphepane with phenylmagnesium bromide and, while not able to isolate the expected tertiary carbinol, obtained a hydrocarbon, $C_{23}H_{24}$, which was found by quantitative hydrogenation to contain one double bond. They considered structure CLXII to be the most probable one for this compound but could not confirm this by oxidation. These authors concluded the spatial model of CLXII to be entirely possible from the standpoint of strain theory. They interpreted Bredt's rule as not applying to CLXII directly, and cited reference 34, in which Bredt presented a somewhat misleading picture of the ring size necessary for a bridgehead double bond (cf. page 244). Asahina and Sano (11) reinvestigated this work and were unable to obtain the hydrocarbon described above, but Bredt's rule was not mentioned. There is evidence, e.g., the data of table 1, that a bridgehead double bond cannot occur in the related (compare page 224) bicyclo[3.2.1] system in accordance with the rule, and it seems improbable that structure CLXII can be either essentially strainless or correct.



Hückel (77) called attention to the fact that the somewhat strained ring system XVa (page 224) is as yet unknown. Attempts to cyclize CLXIIIa via the acid chloride were unsuccessful, although the next higher homolog CLXIIIb and CLXIV yielded the expected tricyclic ketones (32a). The formation of CLXV by a similar route apparently did not occur (78). The analogous bicyclic structure CLXVI was obtained in the dimethylphenol series (page 243); with the nitro substituent the keto form having one bridgehead double bond was reported (page 242).

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THE NAPHTHYRIDINES¹

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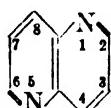
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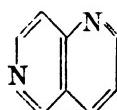
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I. INTRODUCTION

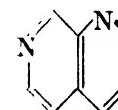
Naphthyridine is the name commonly given to the fused-ring system resulting from the fusion of two pyridine rings through two adjacent carbon atoms, each ring thus containing only one nitrogen atom. This name was suggested by Reissert (57), who, in 1893, made the first representative of the series, since 1,8-naphthyridine was considered to be the naphthalene analog of pyridine. Six naphthyridines are possible:



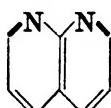
1,5-Naphthyridine



1,6-Naphthyridine



1,7-Naphthyridine



1,8-Naphthyridine



2,6-Naphthyridine



2,7-Naphthyridine

¹ Communication No. 1319 from the Kodak Research Laboratories.

These ring systems have received various names, such as "pyridinopyridines" and "benzodiazines" (see *The Ring Index*, Nos. 1004–1008, inclusive) (51). They may also be named by the "aza" system; i.e., "1,5-diazanaphthalene" may be used instead of "1,5-naphthyridine." However, since all these compounds have been indexed in *Chemical Abstracts* since 1936 under the heading "naphthyridine," this system of nomenclature will be followed in the present review.

The naphthyridine ring systems are usually built up from aminopyridines, by utilizing various cyclization reactions, essentially the same as those employed in quinoline chemistry (Skraup, Doebner-Miller, Doebner, Knorr). In a few instances they have resulted from the degradation of polynuclear compounds or from the ring enlargement of appropriately constituted phthalimides. The literature is scanty, for naphthyridines are not numerous. No 2,6-naphthyridines are known, and only one compound in the 1,7-series has been described (see page 285).

Naphthyridines (pyridinopyridines) undergo some of the reactions characteristic of pyridines. Among these may be mentioned the activity of halogen atoms ortho or para to the ring nitrogen, the ready hydrolysis of an ortho or para amino group to hydroxyl, replacement of ortho or para hydroxyl by chlorine by means of phosphorus pentachloride at an elevated temperature, and easy decarboxylation of acids. No instances of halogenation or sulfonation have been described, and there is but one instance of nitration.

Little is known about the physiological activity and therapeutic value of naphthyridines, only a few having been examined (75).

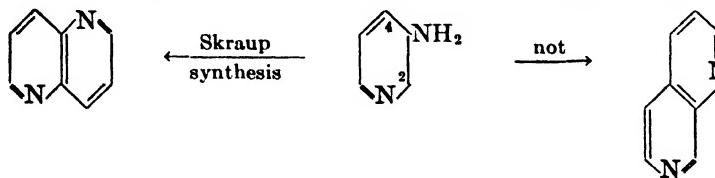
II. 1,5-NAPHTHYRIDINES

This ring system is listed under 1,5-pyridopyridine in the 1936 *Decennial Index* of *Chemical Abstracts* and is called isonaphthyridine in some patents, but in the German literature it is usually given as 1,5-naphthyridine; the latter name is also used by *Chemical Abstracts* after 1936 and in the 1946 *Decennial Index*.

A. PREPARATION

1. Ring closure

Palazzo and Marogna (49) were the first to note that 3-aminopyridine, in contrast to the 2- and 4-aminopyridines, has aromatic characteristics, and they expressed the hope that in the Skraup synthesis it would give 1,5-naphthyridine (I). Fourteen years later it was found that 1,5-naphthyridines are, indeed, obtainable by application of this reaction; thus, 3-aminopyridine gives the base itself (6, 7, 69), as does 3-amino-2-chloropyridine, the halogen being eliminated.



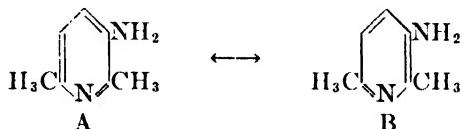
I
1,5-Naphthyridine

3-Aminopyridine

II
1,7-Naphthyridine

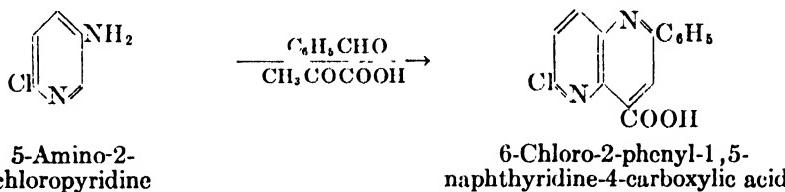
The cyclization takes place through the 2-position, giving 1,5-naphthyridine (I). None of the 1,7-isomer (II), which would result from a ring closure through the 4-position, is obtained.

Even when the 2-position is blocked, as in 3-amino-2,6-dimethylpyridine, no cyclization to the 1,7-naphthyridine ring system occurs. Evidently cyclization of a 3-aminopyridine to the 4-position is difficult. This may be due (a) to failure to achieve the optimum experimental conditions, (b) to side reactions involving the reactive methyl groups, or (c) to a preferred bond position such as shown by the resonance structure B.

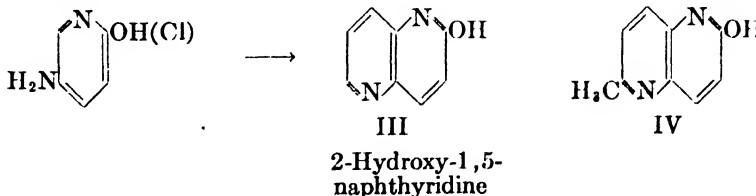


Many years ago Marckwald (37, 39) showed that in the Skraup reaction the new ring is always closed on the other end of the double bond bearing the amino group, and that the presence of a methyl group in that position prevents ring closure. Fieser (15) states that "apparently there is a general disposition for cyclization to occur in such a way that the new ring includes the double bond of the original ring system."

When Doebner's modification of the Skraup synthesis is used, 5-amino-2-chloropyridine, benzaldehyde, and pyruvic acid are said to give 6-chloro-2-phenyl-1,5-naphthyridine-4-carboxylic acid (54, 56, 69), but this statement has been questioned (73).



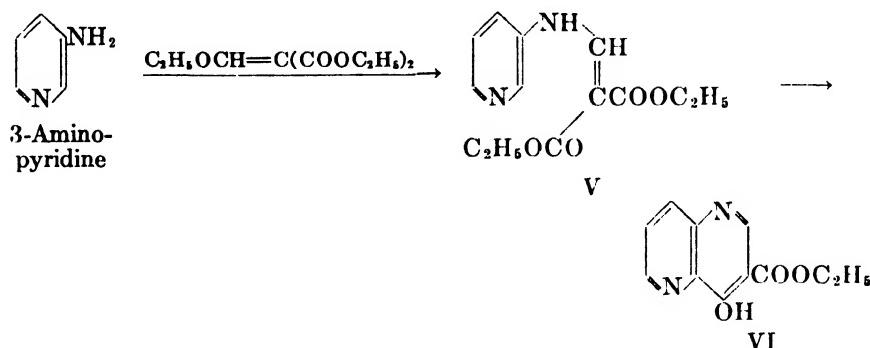
In the Skraup reaction both 5-amino-2-hydroxypyridine and 5-amino-2-chloropyridine give 2-hydroxy-1,5-naphthyridine (III), the chlorine atom undergoing hydrolysis (69).



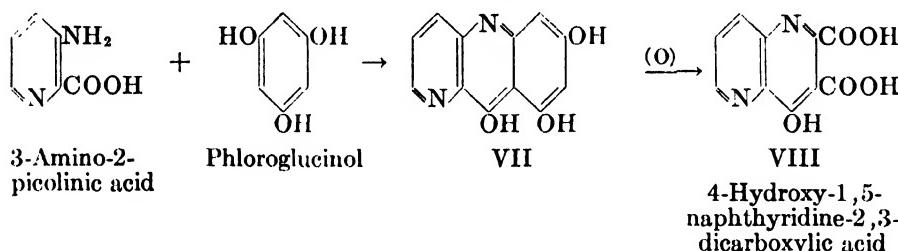
The 2-hydroxy-6-methyl-1,5-naphthyridine homolog (IV) results when para-aldehyde reacts with 5-amino-2-hydroxypyridine (69).

Adaptation of the excellent quinoline synthesis of Price and Roberts (54) is the most practical preparative method. In this reaction, 3-aminopyridine is first

condensed with ethoxymethylenemalonic ester, and the resulting ester (V) is then cyclized to 4-hydroxy-1,5-naphthyridine-3-carboxylic acid ethyl ester (VI) (1, 54a) by heating in Dowtherm A.²



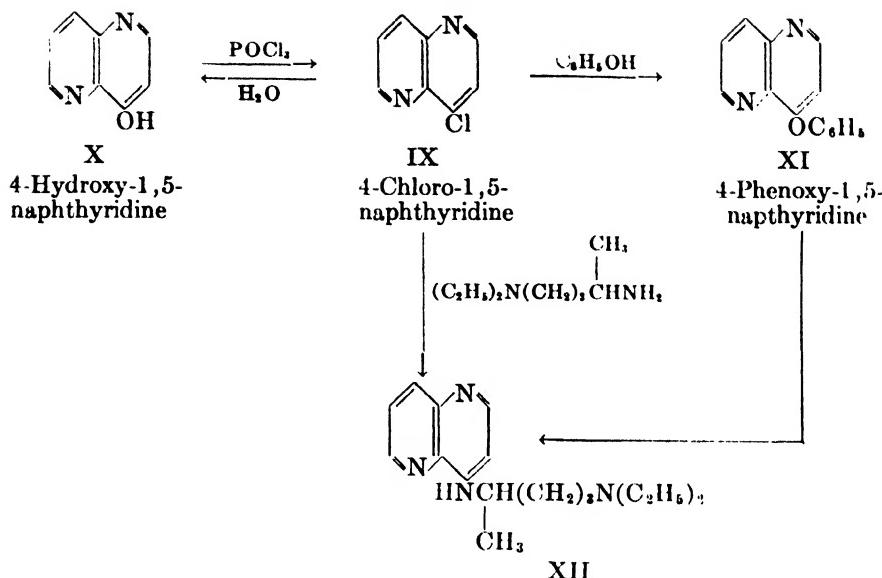
Another synthesis, not of preparative value but used as proof of structure, is the condensation of 3-amino-2-picolinic acid and phloroglucinol, followed by oxidation of the product, 7,9,10-trihydroxy-1,5-diazanthracene (VII) (6, 22), to 4-hydroxy-1,5-naphthyridine-2,3-dicarboxylic acid (VIII).



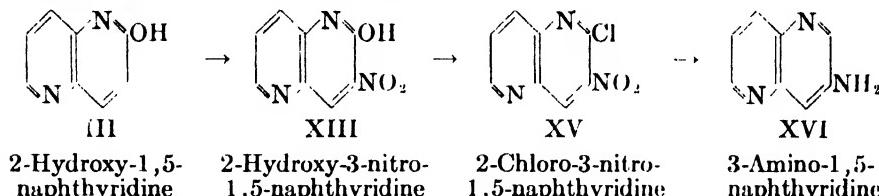
2. Replacement reactions

Once the naphthyridine ring system has been formed by ring closure, derivatives can be prepared by the usual reactions of double decomposition, or by elimination of a group present. The hydroxyl groups ortho or para to the nitrogen atoms are easily replaced by chlorine, using phosphoryl chloride. The chlorine atom, in turn, is available for other reactions of double decomposition, including hydrolysis; the latter was mentioned in one of the preparative procedures just described (page 277). When the 4-chloro derivative (IX) is treated with a large excess of 4-amino-1-diethylaminopentane at 100°C., 4-(4'-diethylamino-1'-methylbutylamino)-1,5-naphthyridine (XII) is obtained in a yield of 90 per cent (1). When the foregoing reaction was carried out in phenol as a solvent, the 4-phenoxy compound (XI) was isolated; it gave the same product (XII) when heated with the aminopentane derivative (1).

² Dowtherm A, a eutectic mixture of diphenyl ether and biphenyl, is used as the solvent, and the reaction temperature is 250°C. The ester concentration is set at 0.25 mole per liter, in order to favor intramolecular ring closure as against polymer formation.

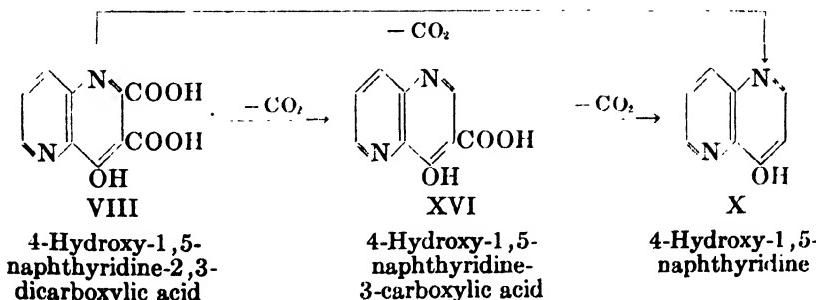


3-Amino-1,5-naphthyridine (XIV) can be obtained by the following series of reactions: 2-hydroxy-1,5-naphthyridine (III) is readily nitrated, the NO_2 group entering in the 3-position (XIII). The hydroxyl group is then replaced by chlorine in the usual way, and the 2-chloro-3-nitro derivative (XV) is reduced catalytically, with loss of the halogen (4, 5).



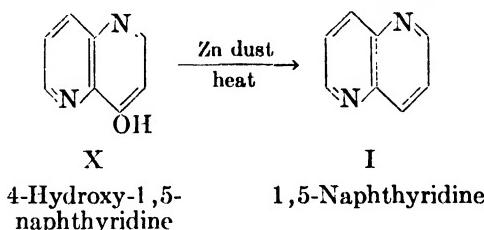
3. Elimination reactions

The most useful elimination reaction is decarboxylation. 4-Hydroxy-1,5-naphthyridine 3-carboxylic acid (XVI), whether obtained by hydrolysis of the



ester (VI) or from 4-hydroxy-1,5-naphthyridine-2,3-dicarboxylic acid (VIII) by partial decomposition, is readily decarboxylated by heating to give 4-hydroxy-1,5-naphthyridine (X) (6, 22, 54); the latter can also be obtained directly from the dibasic acid (VIII) (6, 22).

Hydroxyl groups can be eliminated by the usual zinc dust distillation (6, 22); in this way the free base 1,5-naphthyridine (I) was first obtained. The Skraup reaction is now employed to prepare this substance (page 276).



B. PROPERTIES

1,5-Naphthyridine is a white solid (m.p. 75°C., b.p. 112°C./12 mm.) with a strong tendency to sublime. It turns yellowish in the air. It is soluble in all solvents, including water, and is best recrystallized from petroleum ether or carbon disulfide. The aqueous solution has a bitter, burning taste and a neutral reaction.

The hydroxynaphthyridines have high melting points and often sublime without melting. They are insoluble or sparingly soluble in hot water or hot alcohol, but dissolve in solvents such as chloroform. They have both acidic and basic properties, dissolving in both mineral acids and inorganic alkaline solutions.

While usually slightly colored, the pure naphthyridine derivatives so far described are undoubtedly colorless if protected from aerial oxidation.

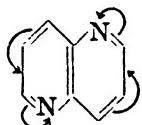
1,5-Naphthyridine forms salts, usually in a 1:1 ratio; among these are a sulfate, picrate, and chloroplatinate. Salts of certain derivatives are oils, but the picrates are usually crystalline.

As pyridinopyridines, naphthyridines might be expected to exhibit the basic properties of pyridine twice. However, salts with one equivalent of acid for each pyridine nucleus have been mentioned only in isolated cases, *viz.*, the dihydrochloride of 1,5-naphthyridine (6) and the trihydrochloride of 3-amino-1,5-naphthyridine (5). It appears possible that neutral salts composed of one mole of base and two equivalents of acid have not been isolated more often because they are more soluble than the basic salts. The observation that the monohydrochloride of 7-carbomethoxy-4-hydroxy-1,6-naphthyridine (page 285) dissolves in excess hydrochloric acid would agree with this suggestion.

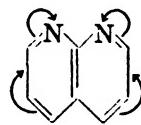
However, there is another possible cause for the failure to observe the formation of neutral salts. In the salt formation of tertiary bases a coördinative link is formed between the nitrogen and the proton of the acid, *i.e.*, a pair of electrons from the nitrogen is shared with the proton. Thus the nitrogen acquires a positive charge and might polarize the remainder of the molecule so that the "lone" pair of electrons on the other nitrogen is now drawn closer into the mole-

cule, with the result that the ability of this nitrogen to form a coördinate link is restricted, i.e., its tendency to salt formation is decreased (36).

A shift of electrons to the nitrogen atoms by resonance of the molecule, however, can increase the tendency to salt formation (opposing the polarization effect). Assuming that the structures with symmetrical distribution of the double bonds are most important, and indicating the resonance by curved arrows, 1,5-naphthyridine can be designated by formula XVII and 1,8-naphthyridine by formula XVIII.



XVII
1,5-Naphthyridine



XVIII
1,8-Naphthyridine

It is evident from the structural formulas on page 275 that a two-step mesomeric shift of electrons to both nitrogen atoms can take place only with these two isomers. With 1,8-naphthyridine, however, the shift would cause an accumulation of electrons on neighboring nitrogen atoms, resulting in a high electric moment for the molecule. Electrostatic interactions, therefore, would tend to counteract the resonance effect. In 1,5-naphthyridine, on the other hand, resonance is unhindered and is strong enough to overcome the polarization effect by salt formation. The fact that salts with two equivalents of acid are reported only for the 1,5-naphthyridines agrees with this electronic explanation.

Substituents which polarize the molecule by attracting electrons diminish the tendency to salt formation. Thus, 2,4-dichloro-1,8-naphthyridine can be separated from the parent compound by extracting the ether solution of the mixture with aqueous picric acid; only the unchlorinated compound goes into the acidic solution (24) (see page 295).

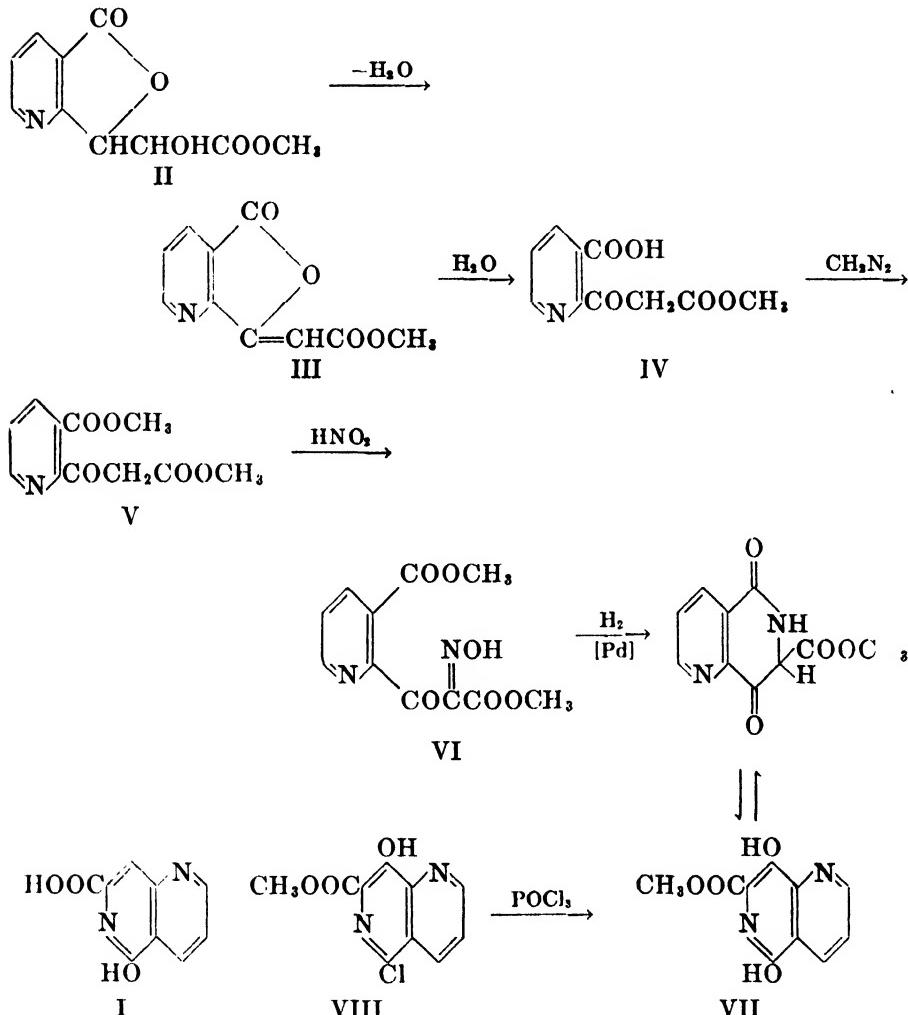
Measurements of electrolytic dissociation in solution and of dipole moments of naphthyridines should furnish valuable information on these compounds.

III. 1,6-NAPHTHYRIDINES

1,6-Naphthyridines cannot be said to be readily accessible substances. The few compounds known have been prepared by reactions involving several steps and have required relatively complex starting materials. In the literature this ring system has been given an alternate, less-favored numbering, and most of the derivatives are listed under 2,5-naphthyridines.

The base itself has not yet been described. Only hydroxy-1,6-naphthyridines, their simple derivatives, and related compounds are known. Rosenheim and Tafel (60) treated the lactone of "pyridylglycerincarboxylic acid" with ammonia, and obtained 5-hydroxy-1,6-naphthyridine-7-carboxylic acid (I), which they called "1-oxo-3-carboxy-2,5-naphthyridine." The reaction is complex, the various steps and proof that the lactone is a γ -lactone were given by Ochiai and

his collaborators (48). Their synthesis is as follows: The methyl ester (II) of the lactone of β -(3-carboxypyridyl-2)glyceric acid is dehydrated to the unsaturated lactone (III); the latter easily adds a molecule of water to give the keto ester (IV), the free carboxyl group of which is then methylated using diazomethane. The resulting methyl ester (V) gives an isonitroso derivative (VI) when treated with acetic acid and sodium nitrite, and upon hydrogenation in the

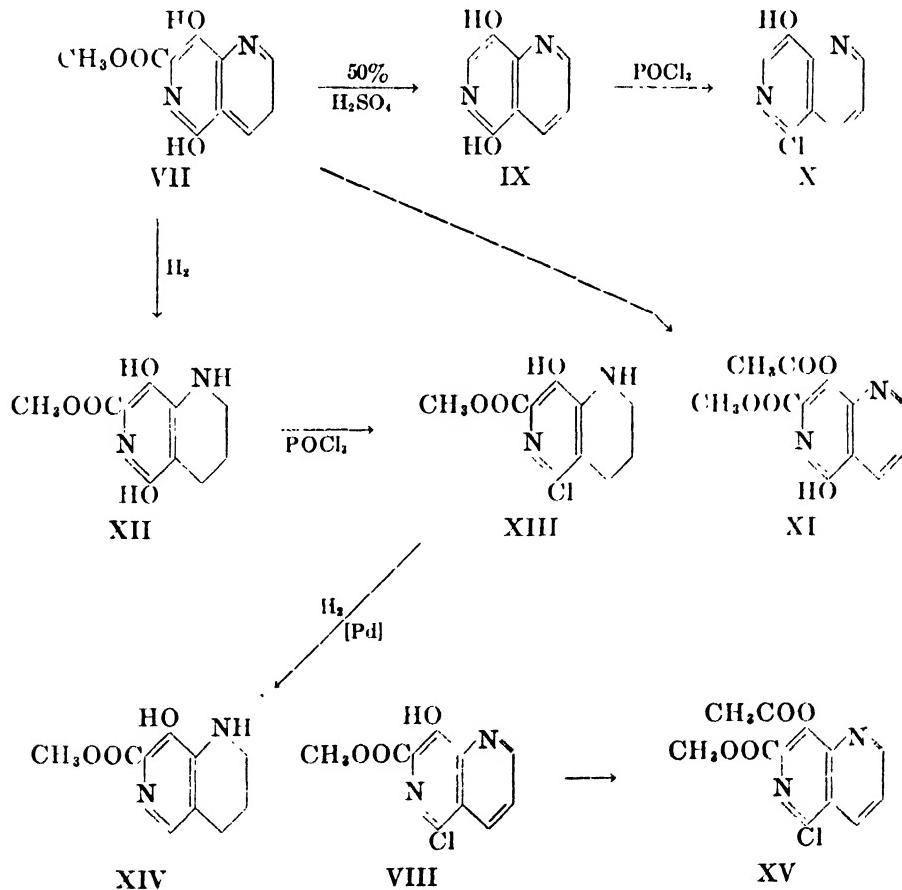


presence of palladium on charcoal the methyl ester of 5,8-dihydroxy-1,6-naphthyridine-7-carboxylic acid (VII) is obtained. Ochiai and coworkers assigned the name "1,4-dioxy-2,5-naphthyridine carbonic acid-(3) methyl ester" to VII. As a lactam it gives a monochloro derivative, 5-chloro-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (VIII) on treatment with phos-

phoryl chloride. The phenolic hydroxyl was detected by the formation of the monoacetate, 8-acetoxy-5-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (XI).

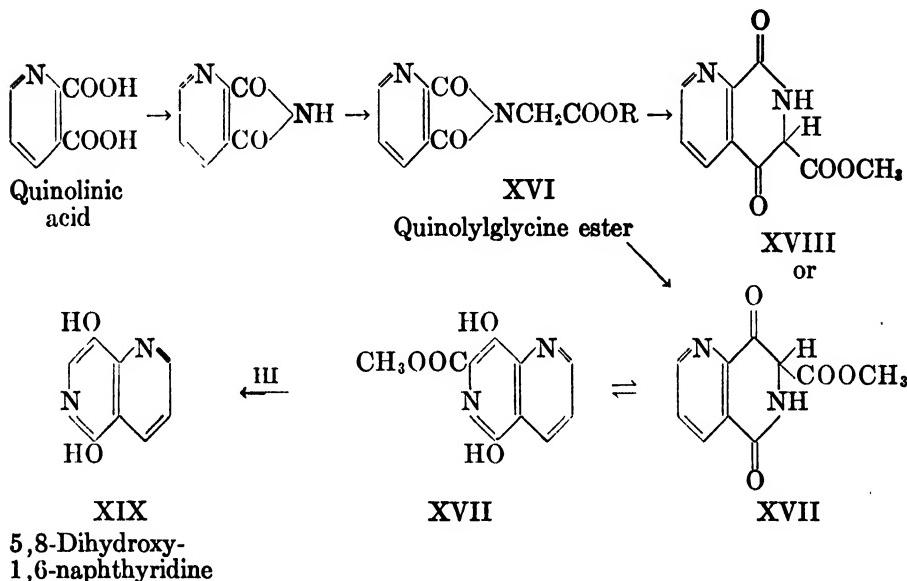
Subsequently (46) the ester VII was both hydrolyzed and decarboxylated with 50 per cent sulfuric acid; 5,8-dihydroxy-1,6-naphthyridine (IX) resulted instead of the anticipated acid (I) of Rosenheim and Tafel (60).

The lactam group in IX was confirmed (48) by preparation of the chloro derivative, 5-chloro-8-hydroxy-1,6-naphthyridine (X), whereas the hydroxyl group in position 8 was detected by formation of an ester, 8-acetoxy-5-hydroxy-1,6-naphthyridine. Upon catalytic reduction four atoms of hydrogen were taken up (46); the tetrahydro derivative, 5,8-dihydroxy-1,2,3,4-tetrahydro-1,6-naphthyridine-7-carboxylic acid methyl ester (XII), likewise gave a 5-chloro derivative, 5-chloro-8-hydroxy-1,2,3,4-tetrahydro-1,6-naphthyridine-7-carboxylic acid methyl ester (XIII). In the latter, the chlorine was replaced by hydrogen upon catalytic reduction, with consequent formation of 8-hydroxy-1,2,3,4-tetrahydro-1,6-naphthyridine-7-carboxylic acid methyl ester (XIV).



Acetylation of the chloro ester (VIII) gave 8-acetoxy-5-chloro-1,6-naphthyridine-7-carboxylic acid methyl ester (XV) (46); this ester (VIII) was also converted to the corresponding amide, 5-chloro-8-hydroxy-1,6-naphthyridine-7-carboxamide.

In 1904 Fels (14) studied the rearrangement of quinolylglycine ester (XVI) in the presence of sodium methoxide; Gabriel and Coleman had previously applied this reagent to phthalimidoacetic ester (16) and to cinchomeronylglycine ester (I, page 287).

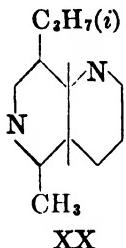


The rearrangement is ambiguous, in that the product may be a derivative of either 1,6-naphthyridine (XVII) or 1,7-naphthyridine (XVIII). Fels attempted to prove the structure of the ester by treatment with hydrogen iodide and red phosphorus, a reaction successfully employed by Gabriel and Coleman with their quinolinic compound, and also by Fels in the 2,7-naphthyridine series (page 286). Fels concluded that the substance was a derivative of the expected naphthyridine ring system because, upon oxidation, the dihydroxy derivative gave a colored product (dimer?) resembling those obtained from analogous compounds both by Fels in the 2,7-series and by Gabriel and Coleman. However, with this ester only hydrolysis and decarboxylation to the dihydroxy derivative, 5,8-dihydroxy-1,6-naphthyridine (XIX) took place. Fels also suggested the name "chinopyrin" for the new ring system. Since his structures are written throughout his paper as 1,7-naphthyridines, it would seem that this was his preference; however, he was careful to note that the alternative 1,6-structures were not excluded.

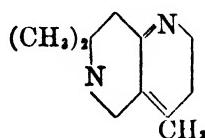
Ochiai and coworkers (45) proved recently that the product was a 1,6-naphthy-

ridine. They prepared the methyl ester by Fels's procedure and showed that it was identical with a specimen obtained by their own procedure (page 283) (i.e., XVII = VII). Hence the two dihydroxynaphthyridines shown in formulas IX and XIX also are identical.

The Japanese authors carried out these reactions with the ultimate aim of synthesizing a substance, $C_{12}H_{24}N_2$, which they had obtained by degradation of an alkaloid, matrin, and which they concluded was either 8-isopropyl-5-methyl-decahydro-1,6-naphthyridine (XX) or the 7-methyl isomer (48).



XX



XXI

A 1,6-naphthyridine structure has been assigned to one other substance. When β -ethoxyethyl β' , β' -dimethylvinyl ketone was shaken with 25 per cent ammonium hydroxide, a base, $C_{11}H_{18}N_2$, was found among the products; the authors (44) represented it as 4,7,7-trimethylhexahydro-1,6-naphthyridine (XXI). No proof of structure has been given for either base (XX or XXI).

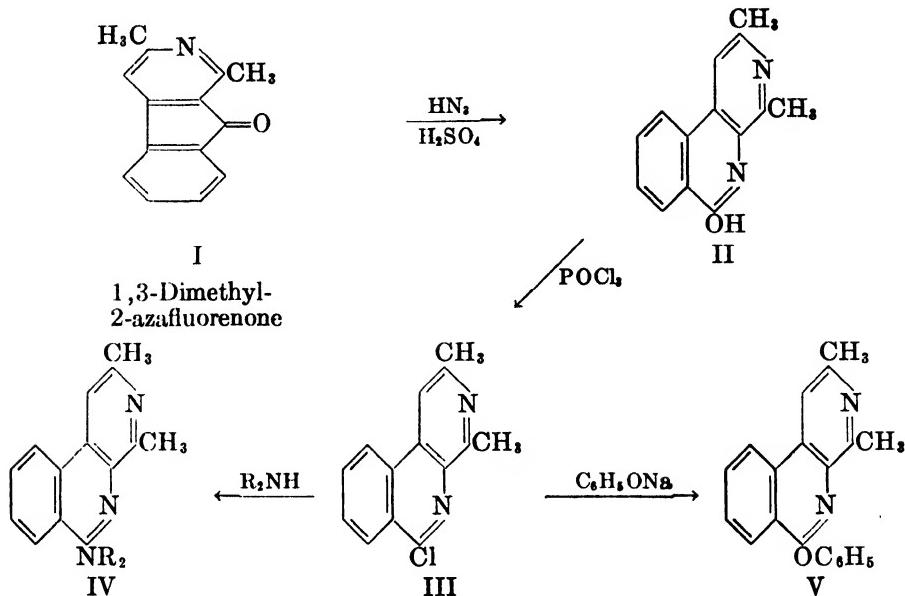
5,8-Dihydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (VII) forms highly colored salts with mineral acids, platinic and gold chlorides, and picric acid. The monohydrochloride that first separates when the ester is treated with hydrochloric acid dissolves in an excess of the latter. The ester is acidic enough to dissolve in ammonium hydroxide but, as might be expected, the ammonium salt is readily hydrolyzed, and the ester is precipitated when the ammonia is boiled off. 5,8-Dihydroxy-1,6-naphthyridine (IX) likewise forms colored salts. It gives yellow solutions in acids and alkalies, including sodium carbonate solution. It is soluble in hot water, but it cannot be recovered; the aqueous solution turns brown in the air. A monohydrochloride of the reduction product (XII) has also been described.

IV. 1,7-NAPHTHYRIDINE

No simple 1,7-naphthyridine is known. A brief description of a benzo derivative may be given at this point.

1,3-Dimethyl-2-azafluorenone (I) undergoes a ring enlargement when submitted to the Schmidt reaction (hydrazoic acid and a catalyst) (19, 20, 63, 64, 71, 72). Phosphoryl chloride converts the resulting lactam, 3,4-benzo-2-hydroxy-6,8-dimethyl-1,7-naphthyridine or 6-hydroxy-2,4-dimethyl-3,5-diazaphenanthrene (II), to a 2-chloro derivative (III); the chlorine atom can be replaced by NH_2 , NR_2 , and OR . The 2-amino (IV: $R = H$), 2-piperidino (IV: $R = C_5H_{10}$), and 2-

phenoxy (V) derivatives have been prepared (52). The 1-carbethoxy derivative of II has also been mentioned (71).



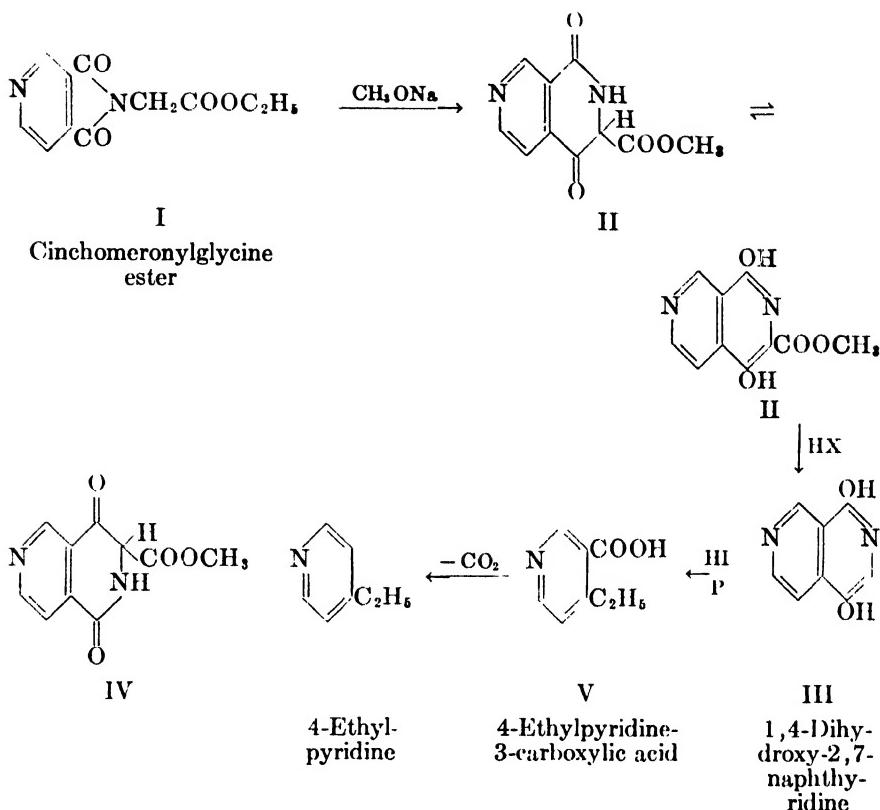
V. 2,7-NAPHTHYRIDINES

The 2,7-diazanaphthalene ring system was given the name "copyrin" by its discoverers, Gabriel and Coleman (16). The base itself is unknown, and but few derivatives have been described.

Gabriel and Coleman adapted their ring enlargement of phthalimidoacetic ester to cinchomeronylglycine ester (I). This reaction, already mentioned (page 284), consists in heating the ester in absolute methanol in the presence of sodium methoxide. A rearrangement takes place, and 1,4-dihydroxy-3-methoxycarbonyl-2,7-naphthyridine (II) is formed; the ethyl ester undergoes transmethylation at the same time. The ester is hydrolyzed and decarboxylated, upon treatment with hydrogen bromide or iodide, to 1,4-dihydroxy-2,7-naphthyridine (III).

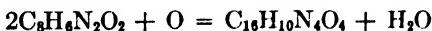
The rearrangement is ambiguous, in that the new ring system could have the two nitrogen atoms in either the 2,7- (II) or the 2,6-position (IV). That the former is correct was shown by degrading the ester, using hydrogen iodide and red phosphorus, in a sealed tube; 4-ethylpyridine-3-carboxylic acid is formed. Upon decarboxylation the latter gives 4-ethylpyridine; hence the acid is V and the starting ester must have structure II.

Both of the 2,7-naphthyridine derivatives shown in formulas II and III are yellow. They are sparingly soluble in water, but the aqueous solutions rapidly become yellow brown. The dihydroxy compound (III) is soluble in hot alcohol but insoluble in acetone and ethyl acetate. Its suspension in pseudocumene turns brown when heated.



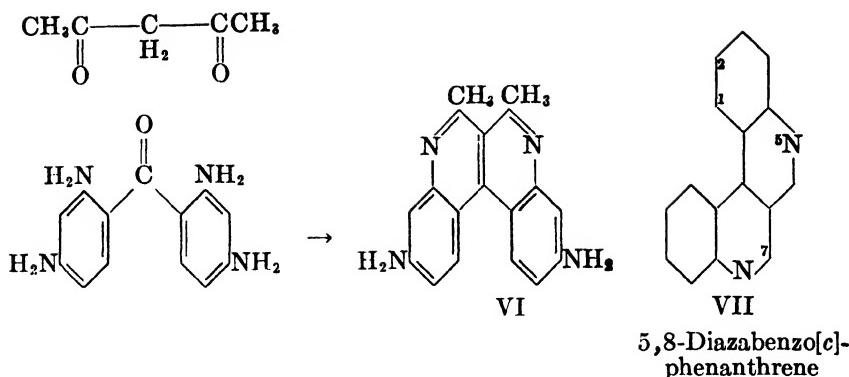
Both substances are soluble in dilute mineral acids and bases, including carbonates. The ester dissolves in ammonium hydroxide, but separates when the solution is heated to expel the ammonia.

They form highly colored salts which have decomposition points above 200°C . A picrate was prepared from 1,4-dihydroxy-2,7-naphthyridine (III). The latter was oxidized to a colored base (dimer?) according to the equation:



Nothing is known about this new base, except that it was isolated as a dihydrochloride.

A "dibenzocoryrin" (VI) has been obtained from 2,4,2',4'-tetraaminobenzophenone and acetylacetone (17) (see page 288). A few other derivatives of this system are known, being obtained from 2,2'-diaminobenzophenones and 1,3-diketones (30); they are not included here since they really belong to the tetracyclic system, 5,8-diazabenzoc[*c*]phenanthrene (VII), shown as Ring Index No. 2710 (51).

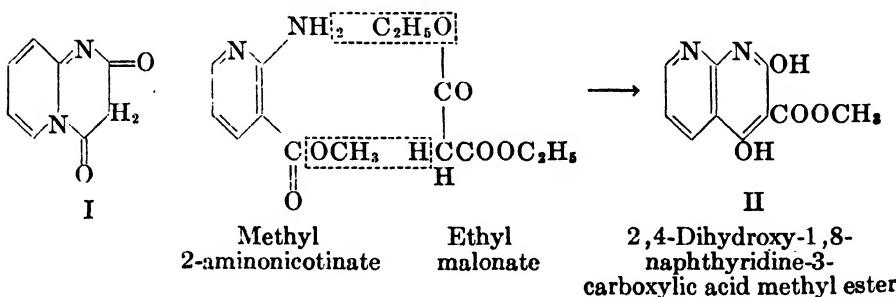


More is known about the 1,8-naphthyridines than about all the other naphthyridines combined. Most of the work dates from the discovery that 2-aminopyridines can be easily and cheaply prepared by the action of sodium amide on pyridine bases. However, it has been shown that many of the heterocyclic compounds prepared from 2-aminopyridine are not naphthyridines (Section VI, C). 2,6-Diaminopyridine, however, is readily cyclized to derivatives of 1,8-naphthyridine: this ring closure takes place through the 3-position, whereas with 2-aminopyridine the ring closes through the 1-position.

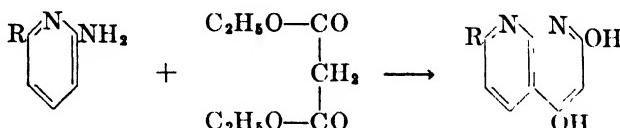
A. PREPARATION

1. Ring closure

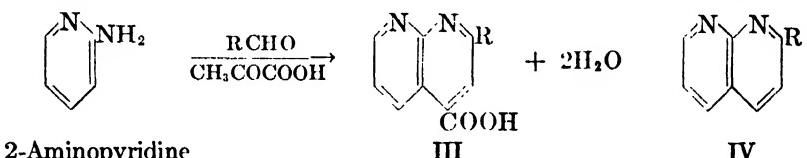
(a) Most attempts to prepare the 1,8-naphthyridine ring system from 2-aminopyridines have been unsuccessful, because the ring closure takes place through the ring nitrogen. Among these may be mentioned the Skraup (38, 40), Doebner-Miller (38, 61, 62), Knorr (12), and Price-Roberts (54) syntheses (see Section VI, C). Likewise, ethyl malonate and 2-aminopyridine give a 1,4-diazanaphthalene derivative (I) (8), but, with methyl 2-aminonicotinate, ring closure takes place through the carboxyl group and 2,4-dihydroxy-1,8-naphthyridine-3-carboxylic acid methyl ester (II) is obtained (it should be noted that there has also been an ester interchange) (23).



A recent study (29) of the reaction between 2-aminopyridine and malonic ester has shown that 1,8-naphthyridines are formed in a few instances only. The essential feature is the presence of a methyl (5 per cent), acetamido (85 per cent), ethoxy (92 per cent), or amino (100 per cent) group (the yields are given in parentheses).



It has been stated that the Doeblner reaction, when applied to 2-aminopyridine, gave 2-substituted 1,8-naphthyridine-4-carboxylic acids (III), from which the parent bases (IV) were obtained upon decarboxylation (41, 42).



2-Aminopyridine

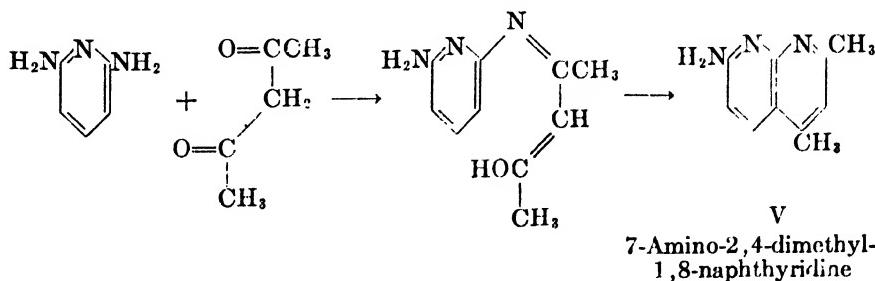
III

IV

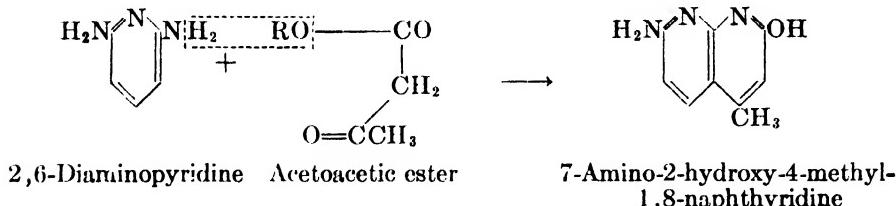
R = C₆H₅—, o-NOOC₆H₄—, p-CH₃OC₆H₄—, p-(CH₃)₂NCO₆H₄—, C₆H₅CH₂CH₂—, C₆H₅CH=CH—.

This reaction needs confirmation, for in all other ring-forming reactions 2-aminopyridine gives rise to 1,4a-diazanaphthalene derivatives having a nitrogen atom common to both rings ("shared N"), and not 1,8-naphthyridines (see Section VI, C, pages 299 and 301).

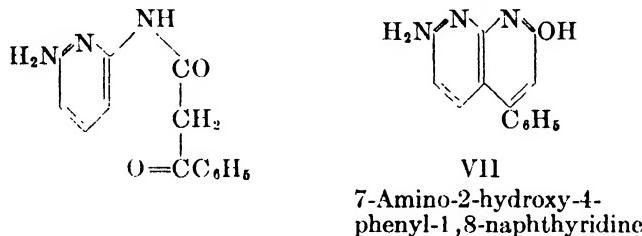
(b) Although the Skraup reaction is of no value with 2,6-diaminopyridine, its various modifications have been very useful in obtaining 1,8-naphthyridine derivatives; all of the latter have an amino group in the 7-position. By Knorr's procedure, for example, acetylacetone and 2,6-diaminopyridine give 7-amino-2,4-dimethyl-1,8-naphthyridine (V) (31, 35, 47). Benzoylacetone gives the corresponding phenyl analog (53). The yield, which is only 15–25 per cent when zinc chloride is used as condensing agent, or 60–70 per cent with concentrated sulfuric acid (53), is raised to 85 per cent when phosphoric acid is employed (3). The intermediate anil has been isolated and cyclized (3).



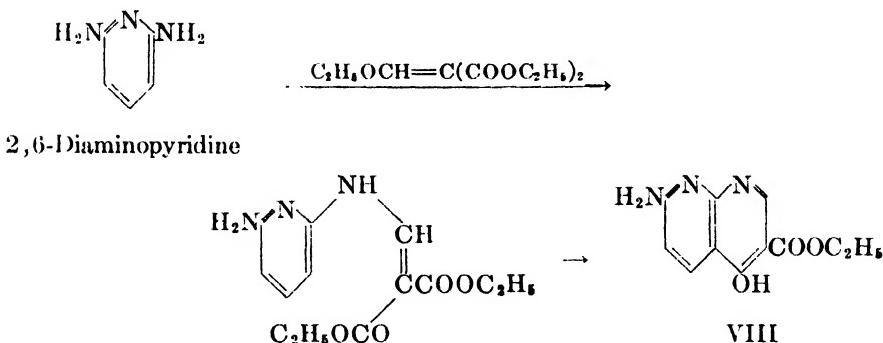
Acetoacetic ester and ethyl β -aminocrotonate (or 2,6-diaminopyridine) react easily to give 7-amino-2-hydroxy-4-methyl-1,8-naphthyridine (VI) (18, 53, 68), while ethyl α -ethoxalylpropionate gives 7-amino-4-hydroxy-3-methyl-1,8-naphthyridine-2-carboxylic acid ethyl ester (18).



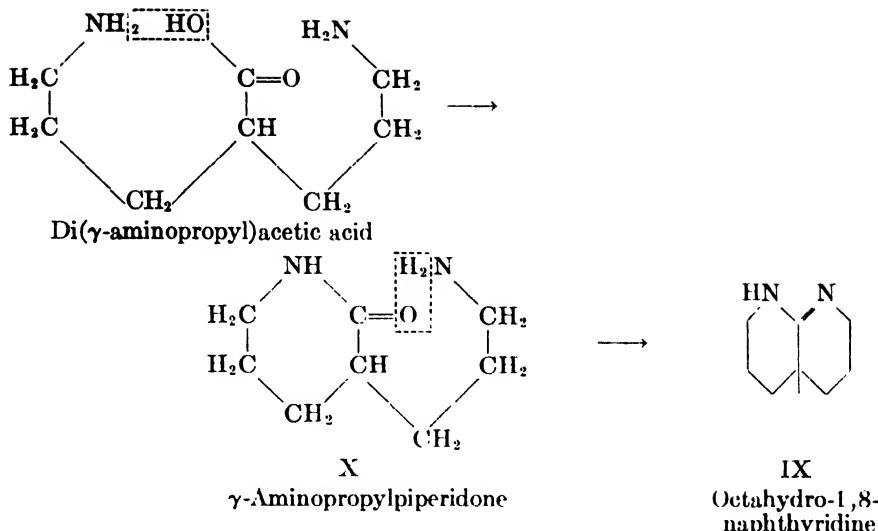
The phenyl homolog (VII) is obtained by the use of benzoylacetic ester; in this case it is possible to isolate the intermediate open-chain acetamide (32, 33).



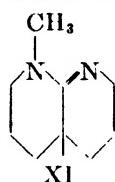
7-Amino-4-hydroxy-1,8-naphthyridine-3-carboxylic acid ethyl ester (VIII) is prepared by the Price-Roberts reaction, using 2,6-diaminopyridine and ethoxy-methylenemalonic ester (54).



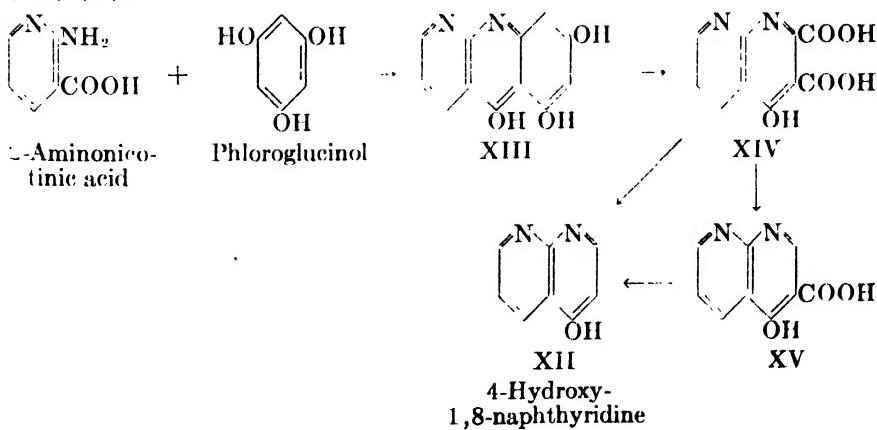
(c) Reissert (57) heated di(γ -aminopropyl)acetic acid and obtained a very small amount of the base, octahydro-1,8-naphthyridine (IX). Subsequently (58) the yield was improved and the intermediate product, γ -aminopropylpiperidone (X), was isolated.



Methylation of the base with methyl iodide yielded the 8-methyl homolog (XI).



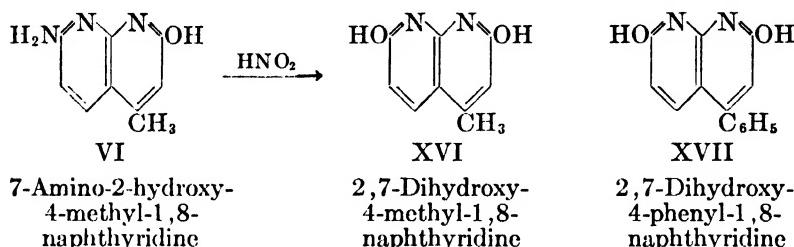
(d) 4-Hydroxy-1,8-naphthyridine (XII) has been obtained from 2-aminonicotinic acid and phloroglucinol, by oxidizing the primary condensation product (XIII) and decarboxylating the resulting acids, 4-hydroxy-1,8-naphthyridine-2,3-dicarboxylic acid (XIV) and 4-hydroxy-1,8-naphthyridine-2-carboxylic acid (XV) (70).



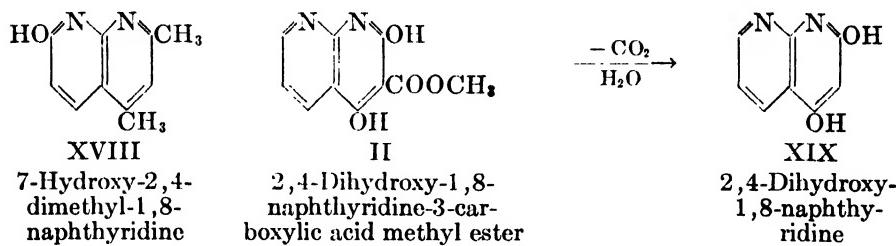
This series of reactions has its analogy in the 1,5-naphthyridines (page 278).

2. Replacement reactions

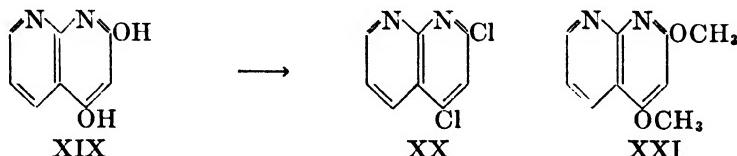
As was noted with the 1,5-naphthyridines, once the ring has been closed, the substituent groups can be replaced by others or eliminated. The 7-amino-1,8-naphthyridines undergo some of the reactions of the analogous 2-aminopyridine. Thus, the amino group in VI is converted to a hydroxyl group by treatment with nitrous acid, giving 2,7-dihydroxy-4-methyl-1,8-naphthyridine (XVI) (31, 32, 33, 68). 2,7-Dihydroxy-4-phenyl-1,8-naphthyridine (XVII) is similarly ob-



tained from the corresponding aryl derivative (VII) (32), whereas 7-hydroxy-2,4-dimethyl-1,8-naphthyridine (XVIII) arises from the amine (V). 2,4-Dihydroxy-1,8-naphthyridine (XIX), however, is obtained (23) by the hydrolysis and decarboxylation of the ester (II).

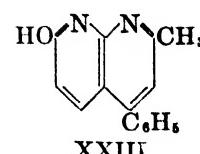
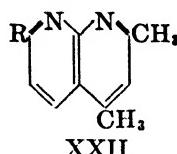
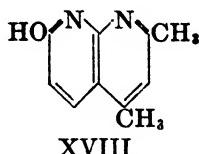


In hydroxy-1,8-naphthyridines, treatment with phosphoryl chloride and/or phosphorus pentachloride brings about a replacement of the hydroxyl group by chlorine in the 2-, 4-, 5-, and 7-positions.



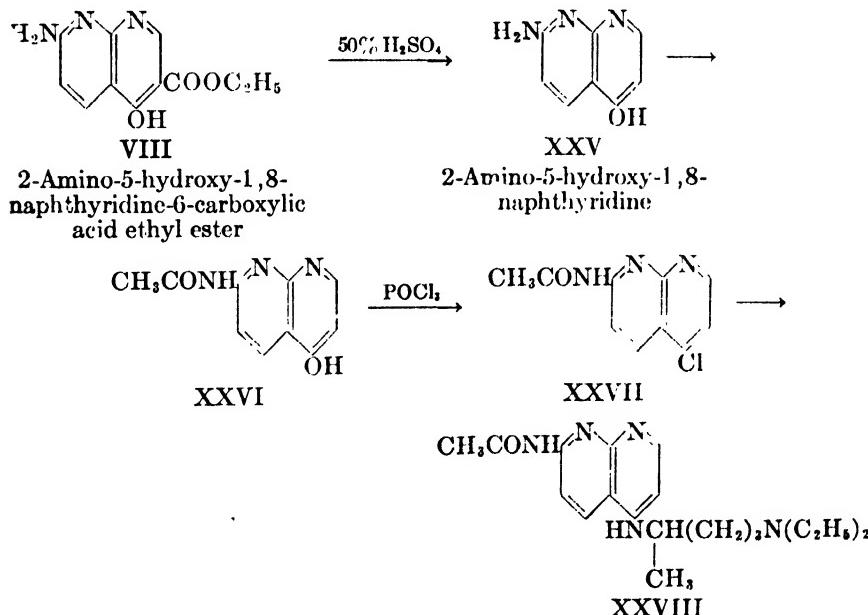
This is a most useful reaction, for the chlorine atoms are available for reactions of double decomposition; in this way substituted amines, hydrazines, and ethers can be obtained (23, 31, 34). For instance, 7-hydroxy-2,4-dimethyl-1,8-naphthyridine (XVIII) has been transformed into the 7-chloro, 7-ethoxy, 7-benzyloxy, 7-benzylamino, and 7-hydrazino derivatives (XXII) (35), while the 4-phenyl-

analog (XXIII) has given 7-chloro, 7-anilino, 7-piperidino, and 7-phenoxy derivatives (53).



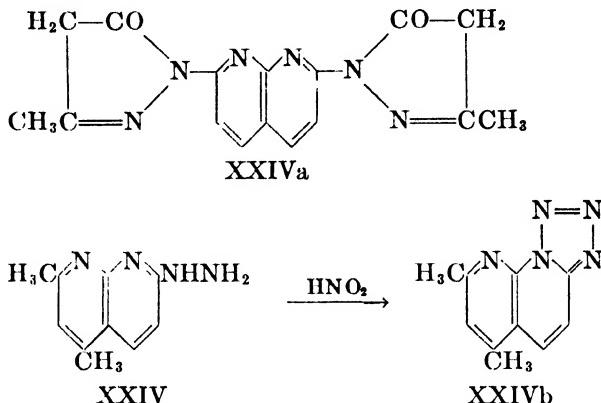
The amino group in 7-amino-2-hydroxy-1,8-naphthyridine is acetylated preferentially (53), but attempts to acylate it with *p*-acetaminobenzenesulfonyl chloride were unsuccessful (53). 7-Acetamino-2-hydroxy-4-methyl-1,8-naphthyridine has been transformed, by reactions similar to those just described, into 2-chloro, 2-arylamino,³ 2-piperidino,³ and 2-phenoxy derivatives (53).

The preparation of an antimalarial drug (XXVIII) illustrates the combination of several of these reactions (1). 2-Amino-5-hydroxy-1,8-naphthyridine-6-carboxylic acid ethyl ester (VIII) is hydrolyzed and decarboxylated with 50 per cent sulfuric acid to give 2-amino-5-hydroxy-1,8-naphthyridine (XXV). After the amino group has been protected by acetylation, the amide (XXVI) is heated with phosphoryl chloride, and the chloro derivative (XXVII) is then converted to the drug, 4-(4'-diethylamino-1'-methylbutylamino)-7-acetamido-1,8-naphthyridine (XXVIII) by a double decomposition with 1-diethylamino-4-aminopentane.

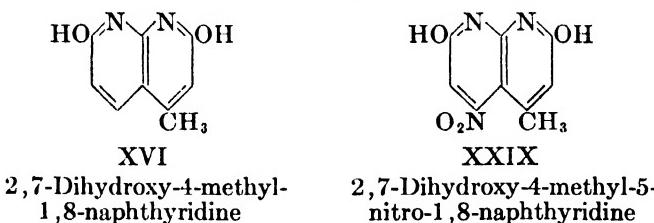


³ The acetyl group is removed by hydrolysis in these instances.

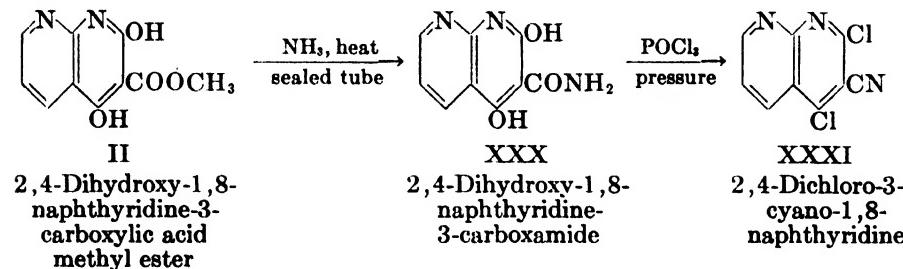
The hydrazines (XXIV) react with aldehydes and ketones to give hydrazones (35); with ethyl acetoacetate, the dihydrazine (XLVI) (page 298) forms a dipyrzalone (XXIVa) (3). Tetrazoles (XXIVb) result when the hydrazines are treated with nitrous acid (35, 68); this reaction is used in proving structures (page 298).



A single instance of nitration has been reported (31); 2,7-dihydroxy-4-methyl-1,8-naphthyridine (XVI) gives a mononitro derivative (XXIX). The location of the nitro group was not determined, but since the statement was made that it could not be ortho to either hydroxyl group, only the 5-position remains.

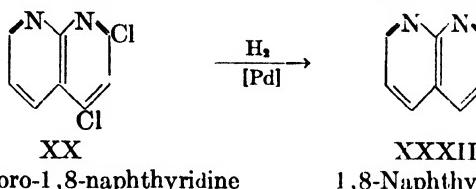


One cyano-1,8-naphthyridine is known (24). The dihydroxy ester (II) was converted to the amide by heating with ammonia in a sealed tube. The 2,4-dihydroxy-1,8-naphthyridine-3-carboxamide (XXX) was then treated with phosphoryl chloride under pressure, with consequent formation of 2,4-dichloro-3-cyano-1,8-naphthyridine (XXXI).



The naphthyridine bases themselves have nearly all been obtained from the chloro compounds by catalytic hydrogenation. Since the reaction is seldom restricted to replacement of the chlorine atom, mixtures result from which the pure bases can be isolated only after tedious manipulation.

1,8-Naphthyridine itself (XXXII) has been obtained by this procedure from 2,4-dichloro-1,8-naphthyridine (24, 25). It is interesting to note that the use of iron and acid, zinc dust and aqueous alcohol, hydrogen and phosphonium iodides,

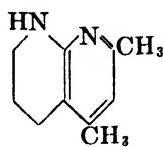


and zinc dust distillation did not give the base. In one instance, hydrogen iodide brought about hydrolysis, the chlorine being replaced by a hydroxyl group (68). 4-Methyl- and 2,4-dimethyl-1,8-naphthyridines are also known (43, 47).

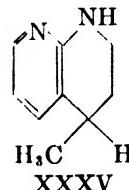
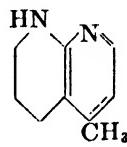
3. Addition reactions

(a) Hydrogenation

By an appropriate choice of catalysts and conditions, hydrogenation can be carried beyond the simple replacement of chlorine by hydrogen; di- and tetrahydronaphthyridines can thus be obtained (47, 68). 2,4-Dimethyl-1,8-naphthyridine gives a single tetrahydro derivative (XXXIII), whereas the 4-methyl analog gives two (XXXIV and XXXV) in a ratio of 4:1 (47). While it has not been conclusively proved, the available evidence indicates that the hydrogen is on the rings, as shown in the structural formulas. The difference in the behavior of the mono- and dimethylated 1,8-naphthyridines on partial reduction is attributed, by Mangini and Colonna (35), to their nuclear configuration. In the dimethyl derivative an aromatic-centered bond is stabilized by the two methyl groups; hence reduction occurs only in the unsubstituted pyridine ring.



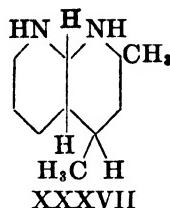
2,4-Dimethyl-5,6,
7,8-tetrahydro-1,8-
naphthyridine



Catalytic hydrogenation stops at the tetrahydro stage, but by means of sodium and amyl alcohol the 4-methyl- and 2,4-dimethyldecahydro-1,8-naphthyridines (XXXVI and XXXVII) are obtained (47).



4-Methyldecahydro-
1,8-naphthyridine



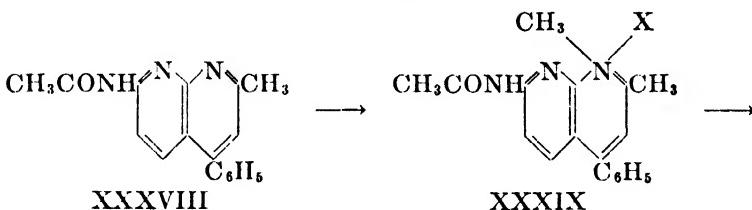
2,4-Dimethyldecahydro-
1,8-naphthyridine

Hydrogenation of 7-hydroxy-2,4-dimethyl-1,8-naphthyridine (XVIII) gives a dihydro derivative in which the location of the hydrogen has not been determined (47); likewise, the reduction of 2,7-dichloro-4-methylnaphthyridine results in the formation of an intermediate monochloro derivative in which the position of the chlorine atoms is unknown (47).

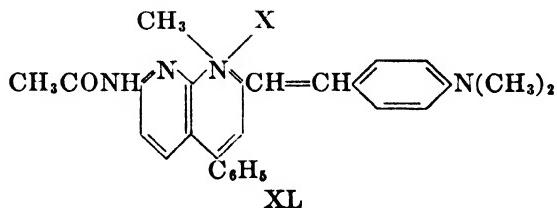
(b) Quaternary salts

Four instances have been recorded in which 1,8-naphthyridines form salts; in all of these the addends have combined in a 1:1 proportion.

7-Acetamino-2-methyl-4-phenyl-1,8-naphthyridine (XXXVIII) adds methyl sulfate to give a salt (XXXIX), which, it was subsequently shown, could be converted to a methiodide and methoperchlorate. The nitrogen in the 1-position is quaternarized, for, when the salt was heated with *p*-dimethylaminobenzaldehyde (and a trace of piperidine), a styryl dye (XL) resulted; the authors were unable to isolate the pure dye, however (53).

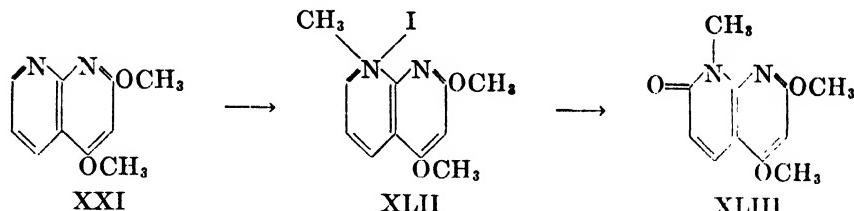


7-Acetamino-2-methyl-
4-phenyl-1,8-naphthyridine



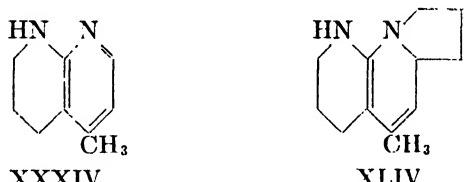
1,8-Naphthyridine adds one equivalent of methyl iodide. The methiodide, when heated, is decomposed, and the 1,8-naphthyridine is regenerated (24) in unstated yield. This is an unexpected result, for the usual behavior of such salts on heating is to give rise to nuclear-alkylated bases and hydrogen iodide.

2,4-Dimethoxy-1,8-naphthyridine (XXI) also forms a monomethiodide (XLII). In this case, the nitrogen in the 8-position is quaternarized, because oxidation with alkaline ferricyanide gives 2,4-dimethoxy-8-methyl-1,8-naphthyridone-7 (XLIII) (26).



2,4-Dimethoxy-1,8-naphthyridine

4-Methyl-5,6,7,8-tetrahydronaphthyridine (XXXIV) adds one equivalent of chloroacetone; when heated with dilute sodium carbonate, the addition product is changed into a noncrystalline material. The latter gives a blue color in the Ehrlich reaction with *p*-dimethylaminobenzaldehyde. The authors consider this characteristic of the indolizine ring, and tentatively suggest an indolizine structure (XLIV) (47).



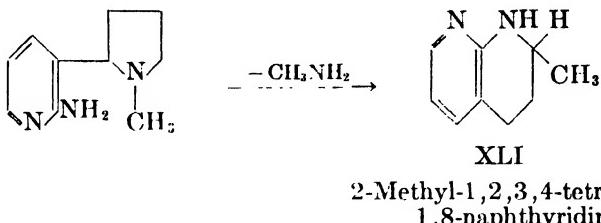
4-Methyl-5,6,7,8-tetrahydro-1,8-naphthyridine

4. Miscellaneous

Clemo and Swan (11) obtained a base, C₉H₁₂N₂, formed during a dehydrogenation of 2-aminonicotine. The properties of this base are as follows: It has one secondary and one tertiary nitrogen, for it gives a nitroso derivative, and an amide, insoluble in sodium hydroxide, with *m*-nitrobenzenesulfonyl chloride. It gave monoacetyl and monobenzoyl derivatives, a monomethiodide, a picrate, and a picrolonate. It could not be catalytically reduced further nor be dehydrogenated⁴ by selenium at 280°C. or 330°C., and was unchanged by fusion with potassium hydroxide at 280°C. Upon oxidation by alkaline permanganate, 2-aminonicotinic acid resulted.

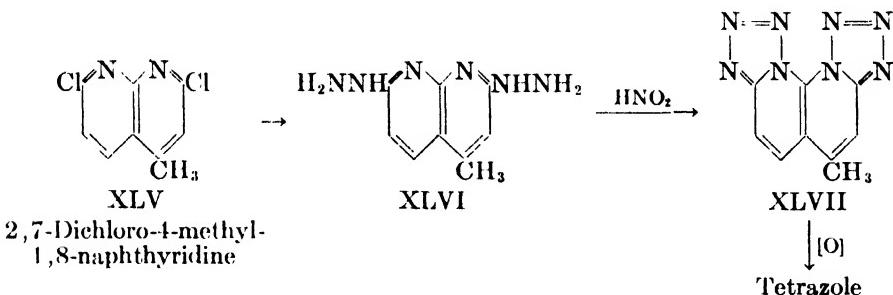
⁴ These authors cite an inaccessible communication by Koller and Kamiller (27) in which it is shown that dehydrogenation over palladium at 220°C. of decahydro-1,8-naphthyridine only goes as far as the tetrahydro derivative and then stops.

On the basis of this evidence the authors ascribe the structure 2-methyl-1,2,3,4-tetrahydro-1,8-naphthyridine (XLII) to the base, and suggest that its formation has taken place by a ring opening and closure, with elimination of methylamine.



B. PROOF OF STRUCTURE

The methods of synthesis by ring closure in some cases leave little doubt as to the presence of the 1,8-naphthyridine ring, but the derivatives obtained from 2,6-diaminopyridine might have other structures. The presence of the naphthyridine nucleus was shown in two cases by the formation of a tetracyclic system containing tetrazole rings (32, 34). Thus, 2,7-dichloro-4-methyl-1,8-naphthyridine (XLV) was converted to 2,7-dihydrazino-4-methyl-1,8-naphthyridine (XLVI) by a double decomposition reaction; with nitrous acid, the dihydrazine gave the tetracyclic base XLVII, which was oxidized to tetrazole (68).



The phenyl analog of XLVII has also been prepared (32, 34).

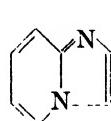
Lappin (28) has recently made a study of the cyclization of certain 2-amino-pyridine derivatives. There were two different types of products: the one commonly formed (the "normal" reaction) was a 1,4a-diazanaphthalene derivative (XLIX), whereas in two instances only, derivatives of 1,8-naphthyridine resulted. He was able to relate mode of ring closure to nature of substituent, and demonstrated that the presence of electron-releasing groups in position 6 of the pyridine ring was essential for naphthyridine formation. The groups so far found to be effective in this way are amino, ethoxy, and methyl. Lappin states: "It seems most probable, therefore, that the formation of 1,8-naphthyridines is due to prevention of ring closure at the 1-position by the ortho effect of the 6-substitu-

ent, since the steric requirements of closure at a nitrogen atom might well differ considerably from those at a carbon atom. Activation of the 3-position is in all probability also required."

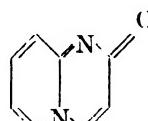
To differentiate between the two ring structures, Lappin used great differences in melting points, relative solubilities, and basic hydrolysis. The 1,4a-diazanaphthalenes have relatively low melting points, are soluble in most of the common solvents, and are easily hydrolyzed to the corresponding 2-aminopyridine derivatives, while the converse is true of the naphthyridines.

C. SUBSTANCES ERRONEOUSLY DESCRIBED AS 1,8-NAPHTHYRIDINES

As already mentioned (page 289), it appears that when 2-aminopyridine and its derivatives react with other substances to form bicyclic systems, ring closure nearly always takes place through the ring nitrogen rather than in the 3-position. Russian chemists, especially Chichibabin (8, 9, 10), have shown that the products are derivatives of pyrimidazole (XLVIII) or 2-keto-1,4a-diazanaphthalene (XLIX). Before these facts were established, some investigators had represented



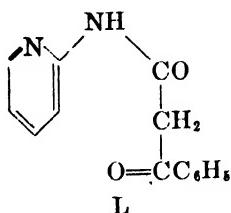
XLVIII
Pyrimidazole



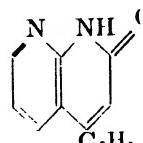
XLIX
2-Keto-1,4a-diazanaphthalene

their reaction products as derivatives of 1,8-naphthyridine. All such instances are collected in this section, and the corrected explanations are given in some detail. It has been pointed out (53) that "2-aminopyridine behaves as a cyclic amidine in these reactions, and on electrochemical grounds alone, its conversion into a 1,8-naphthyridine appears highly improbable."

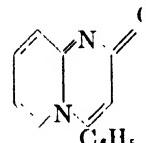
The first instance of this kind was recorded in 1911 by Palazzo and Tamburini (50), who dehydrated the benzoylacetamide (L) formed from 2-aminopyridine and benzoylacetic ester and represented the product as the naphthyridone shown in formula LI.



L

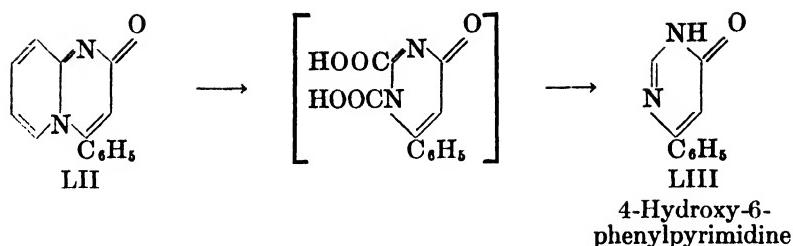


LI



LII

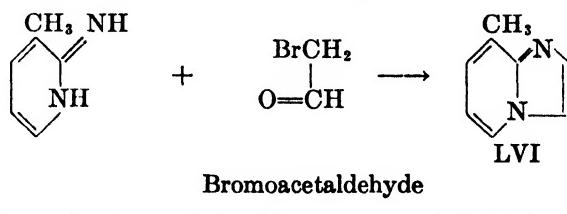
Seide (67) showed that the so-called naphthyridone (LI) is really a diazanaphthalene (LII), having one nitrogen atom common to both rings, by oxidizing it to the known 4-hydroxy-6-phenylpyrimidine (LIII).



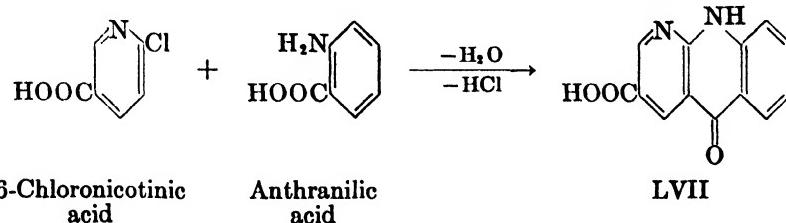
Khitrik (21) examined the reaction products obtained by the interaction of 2-aminopyridine and acetoacetic ester with great care, in view of the contradictory claims in the literature (12, 50), and showed that the base, $C_9H_8N_2O$, is not a methylnaphthyridine (LIV) but a diazanaphthalene (LV).



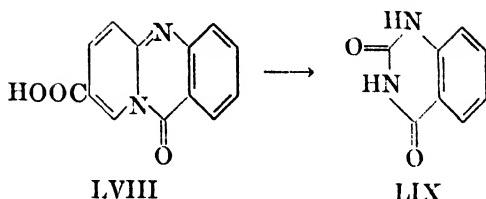
As evidence for the synthesis of 2-amino-3-methylpyridine, Räth (55) heated the substance in a sealed tube with bromoacetaldehyde (as bromoacetal) and obtained an oily product that was stated to be "1,2-dihydronephthyridine." Both Chichibabin (10) and Seide (68) disputed this, and the former was able to show that the product was a pyramidazole base (LVI).



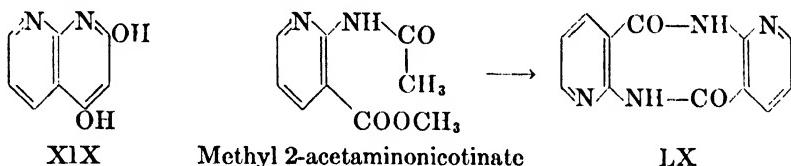
Reissert (59) ascribed a naphthyridine structure (LVII) to a substance obtained by the interaction of 6-chloronicotinic and anthranilic acids.



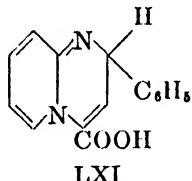
Seide (65, 66) corrected this also; he oxidized the product (LVII), obtaining the quinazolone LIX, from which it was obvious that the acid has the structure shown in formula LVIII.



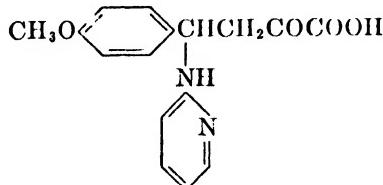
Seide further attempted to prepare 2,4-dihydroxy-1,8-naphthyridine (XIX) by an intramolecular ring closure with methyl 2-acetaminonicotinate, but obtained only the dilactam LX.



In view of these numerous instances, it is somewhat surprising to find in recent publications (41, 42) that 2-aminopyridine is stated to give derivatives of 1,8-naphthyridine in the Doebner reaction (page 289). One would have expected that the product would be a 1,4a-diazanaphthalene (LXI) (2, 53).



Attempts to repeat this work have been unsuccessful (2). Although the substances which were obtained had decomposition points in the ranges stated, they proved to be the 2-aminopyridine addition products of the benzalpyruvic acids; e.g.,



from anisaldehyde.

D. MECHANISM OF RING CLOSURE⁵

It is noteworthy that the condensation products of 2-aminopyridine close the ring through the nuclear nitrogen and form a 1,4a-diazanaphthalene (pyrido-

* This section was written by A. Weissberger of the Kodak Research Laboratories.

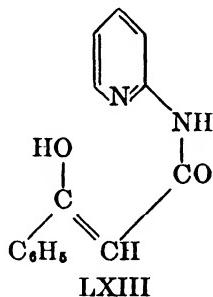
pyrimidine), while the condensation products of 2,6-diaminopyridine close the ring through the carbon atom in position 3 and form 7-amino-1,8-naphthyridine. This behavior may be explained as follows:

The reactivity of the 2-, 3-, and 4-positions of pyridine with electrophilic reagents is lowered by a shift of electrons towards the nitrogen, owing to the inductive effect of the latter. Moreover, positions 2 and 4 suffer further in reactivity with electrophilic reagents by the mesomeric shift of electrons (resonance) indicated in formula LXII (74). Both effects increase the electron density at the nitrogen



LXII

and accordingly the reactivity of the latter with electrophilic reagents. In the ring closure of 2-benzoylacetaminopyridine (LXIII), to choose a definite example, it may be assumed that the enolic hydroxyl group splits off a hydroxyl



2-Benzoylacetaminopyridine

ion, and that the proton is released from the nitrogen, while the electrophilic atom links with the nuclear nitrogen. This bonding is facilitated by the high electron density at the nuclear nitrogen atom. The electron density in position 3, although higher than in positions 2 and 4, appears to be too low to effect a ring closure in position 3.

By analogy with aniline, a free amino group in position 6 should cause an increase in electron density in positions 1, 3, and 5. The last position is of no interest at present, but the course of the ring closure of 2-acetoacetamino-6-aminopyridine seems to indicate that the relative gain in position 3 is greater than that in position 1. This is plausible because the electron density at 1 is already high in the absence of the amino group in 6, while some depletion prevails at 3. A shift of electrons with equal force into both positions will therefore benefit position 3 more than it will position 1. This would explain the effect of the 6-amino group on the course of the ring closure. These conclusions are like those reached independently by Lappin (28) and Hauser (18).

TABLE I
Properties of 1,8-naphthyridine bases

SUBSTANCES	FORMULA NO.	MELTING POINT °C.	BOTTING POINT °C.	ACETYL AND BENZOYL DERIVATIVES	MELTING POINT OF PICRATE °C.	REFERENCES
1,8-Naphthyridine	XXXII	98-99	147-148/0.05 mm.	Benzoyl, m.p. 86-87°C.	207-208 (24, 25)	(47)
4-Methyl-1,8-naphthyridine	XXXV	62-63			204-205 (43, 47)	
2,4-Dimethyl-1,8-naphthyridine	XXXIV	102-103		Acetyl, m.p. 94°C. Benzoyl, m.p. 105-106°C.	248 (47) (68)	
4-Methyl-1,2,3,4-tetrahydro-1,8-naphthyridine	XXXV	62-63				
4-Methyl-5,6,7,8-tetrahydro-1,8-naphthyridine	XXXVI	85-86				
2,4-Dimethyl-5,6,7,8-tetrahydro-1,8-naphthyridine	XXXVII	118	248/754 mm.	Acetyl, m.p. 42-43°C.	207 (47)	
Octahydro-1,8-naphthyridine	IX	67	70-80/0.1 mm.	Acetyl, oil	208-209 (57, 58)	
4-Methyldecahydro-1,8-naphthyridine	XXXVII	87			210 (47)	
2,4-Dimethyldecahydro-1,8-naphthyridine	XXXVII	92-93		Acetyl, b.p. 135-145°C. /0.02 mm.		(47)
8-Methyloctahydro-1,8-naphthyridine	XI		Oil; not isolated			209 (58)

E. PROPERTIES

The 1,8-naphthyridine bases are liquids or low-melting solids, but most of the derivatives have relatively high melting points; the latter are really decomposition points when hydroxyl groups are present in the molecule. They form salts, as usual, with mineral acids and picric acid, as well as double salts with platinum and gold chlorides. One perchlorate has been recorded (47). The salts likewise have decomposition points rather than true melting points; those of the picrates are too close together to be very useful. The properties of the bases are listed in table 1.

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ANTIHISTAMINE DRUGS

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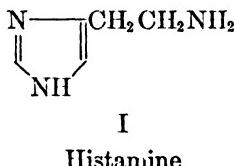
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I. INTRODUCTION

Proof of the concept that histamine (I) or a histamine-like substance is responsible for the various symptoms associated with allergic reactions has



prompted a vigorous search for substances which would antagonize this powerful agent. Several compounds have been developed which are extremely useful in the symptomatic amelioration of these many allergic phenomena (195).

The chemical structures of these antihistaminic drugs vary, yet the prominent compounds exert similar pharmacological and therapeutic action. There is considerable difference in potency, in both animal experiments and clinical tests.

The therapeutic effects of the antihistamine compounds are most evident in the nasal allergies, such as seasonal hay fever and vasomotor rhinitis. Urticaria, angioneurotic edema, motion sickness, the nausea of pregnancy, and serum sickness are other indications which have been relieved (258). Considerable publicity has been given reports of the abortion of the "common cold" (119).

Undesirable side effects, such as sedation, lassitude, and muscular weakness, are produced, the incidence of which varies with the individual drug and the individual patient.

Loew (257) defines antihistaminics as "drugs which are capable of diminishing or preventing several of the pharmacological effects of histamine and do so by a mechanism other than the production of pharmacological responses diametrically opposed to histamine." Consequently, antihistaminic drugs are a special category of spasmolytic drugs, and justification for the name is found in the extraordinarily high specificity of these compounds in antagonizing histamine-induced physiological effects. This specificity is relative and not absolute, for pharmacological experience has proved that absolute specificity is rare and practically unattainable. To a varying extent antihistaminics exert anti-acetylcholine, local anesthetic, sympathomimetic, sympatholytic, antispasmodic, analgesic, and quinidine-like actions (274).

Excellent reviews have appeared (39, 41, 49, 76, 93, 97, 108, 133, 135, 136, 147, 161, 179, 182, 197, 210, 219, 223, 227, 236, 268, 272, 276, 292, 314, 315, 322, 388, 402, 414, 421, 422, 435, 445, 447), outstanding among which are those of Loew (257, 258), Haley (169), Huttner (200, 201), Dunlop (117a), Viaud (443), the book of Bovet and Bovet-Nitti (32), and the Annals of the New York Academy of Sciences (10).

II. HISTORICAL

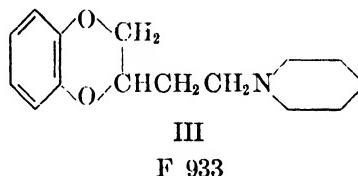
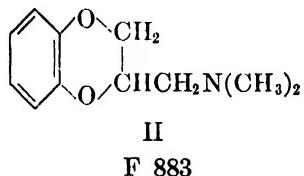
Dale (105) in 1929 noted that the effects of histamine in animals resembled those of anaphylactic shock and advanced the theory that histamine is liberated from the tissues of animals by cell stimulation due to the interaction of an antigen and antibody. Dragstedt (116) compared the physiological effects of histamine with the symptoms observed in asthma, anaphylaxis, and other allergic and pathological conditions and reached the conclusion that, although histamine may not always be the main causative agent, any prevention of its effects would be of great benefit. Rosenthal (233, 234, 372, 374, 375, 376) has published a series of studies designed to prove that histamine or a histamine-like substance is the chemical mediator for cutaneous pain. Thus a large body of evidence has accumulated to indicate that histamine is released in anaphylactic shock and similar reactions in amounts adequate to account for many features of these phenomena (116, 191, 194, 330, 387, 437).

Therapeutic efforts to combat the action of histamine resulted in the use of gradual doses of histamine to desensitize patients and the conjugation of histamine with proteins through azo linkages (138, 389, 450). Feinberg (134), in a report to the Council of Pharmacy and Medicine of the American Medical Association, concluded that the treatments were ineffective. Diamine oxidase (histaminase, Torantil), a kidney enzyme, proved effective in the prevention of the toxic effects of histamine (23, 24, 121, 122), but recent highly purified extracts of this enzyme (318, 417) proved too toxic for clinical use (24, 130, 134, 167, 318, 348, 368). The destruction of histamine appears to be an oxidation phenomenon, but disagreement exists as to whether the enzyme leaves the imidazole ring of histamine intact (417, 418, 451). Several amino acids, including arginine, histidine, and cysteine, inhibit the characteristic action of histamine in laboratory experiments (120). Since 5-10 mg. of arginine monohydrochloride was needed to counteract the effect of 0.02-0.05 microgram of histamine (177, 369, 380), no clinical tests were performed. Amino acids, such as arginine and spermine, are 100,000 to 1,000,000 times less effective than the present synthetic anti-histamine substances.

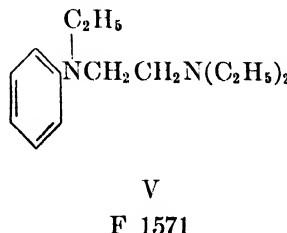
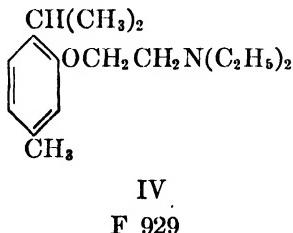
Over 200 compounds other than those included in this review have been tested for activity. Hill and Martin (189) published an extensive review in 1932 which served to emphasize the fact that, although numerous substances had been tested, there were none which could be considered ideal agents for alleviating anaphylactic shock in experimental animals. Some of the more recent substances tested include the following: cardiazole (416), pyridinesulfonamide (410), ascorbic acid, and ascorbates (153, 379), bile acids (128), procaine and quinidine

(118), 2-diethylaminoethanol (89), imidazole (293), nicotinamide (57, 151), pyridylbenzamide (275), cocaine, novocaine, percaine (118, 152, 324, 345), xanthines (129), coramine (164), folic acid (428), vitamin A (13), formaldehyde (217, 218), and various hypotensive agents (14). The claim that ferrous ion is an aid in the prevention of the side effects and potentiates the activity of anti-histamines (409) has been disputed (386). Sympathomimetic and sympatholytic substances have been tested and found relatively active, but their primary action is not against histamine (19, 26, 58, 420).

In 1937 Bovet (38, 408, 433) issued preliminary reports concerning the first effective synthetic antihistaminic drugs. Previous studies of sympathomimetic and sympatholytic poisons, carried out in the Pasteur Institute, had shown that a relationship exists in the pharmacodynamic response between the different series of alkyl aromatic amines: 2-(phenylthio)ethylamine, phenethylamine, 2-phenoxyethylamine, and *N*-phenylethylenediamine. Neither phenylethylenamines nor thioethylenamines counteracted histamine, but the benzodioxans F 883 (II) (33, 140, 141, 145) and F 933 (III) exhibited mild antagonism, prompting further

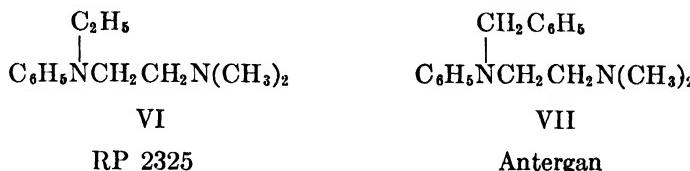


studies of related phenolic ethers. In a series of twenty-one ethers, F 929 (2-isopropyl-5-methylphenoxydiethylamine or 2-thymyloxytriethylamine) (IV) proved to be the most active in alleviating the symptoms of histamine shock in guinea pigs. *N*-Phenylethylenediamines behaved in a similar fashion. Within a series of seventeen amines, F 1571 (*N,N*-diethyl-*N'*-phenyl-*N'*-ethylethylenediamine) (V) proved to be the most active (407), but diverse toxic effects, such as cyanosis, prostration, and convulsions, prohibited the clinical use of these substances. More potent antihistamines resulted from a study of twenty-four



derivatives of F 1571 which had been synthesized by Mosnier (176, 434). The dimethyl homolog of F 1571, *N*-phenyl-*N*-ethyl-*N'*,*N'*-dimethylethylenediamine (VI) (RP 2325), had greater antiasthmatic activity than F 1571 and reduced toxicity. The replacement of the ethyl group by benzyl, giving *N*-phenyl-*N*-benzyl-*N'*,*N'*-dimethylethylenediamine (RP 2339 or Antergan) (VII), resulted

in sufficient improvement to justify the first human therapy. The clinical introduction of this drug was marked with great success and represented, after epinephrine, the first significant step in the chemotherapy of allergic diseases. In



spite of its increased activity and tolerance, Antergan produced a number of unpleasant side effects and was, moreover, ineffective in many patients.

From 1942 on, research in France shifted to the investigation of heterocyclic compounds. Definite progress was made by Horclois (40), who substituted pyridyl for the phenyl group in Antergan. Around 1943 research on heterocycles started in the United States. To American investigators, working mainly with amino-pyridines, the appearance of Bovet's publication (35) dealing with these compounds was a complete surprise. Neoantergan (RP 2786) was shown to possess a remarkable degree of antihistamine potency (34, 35, 40).

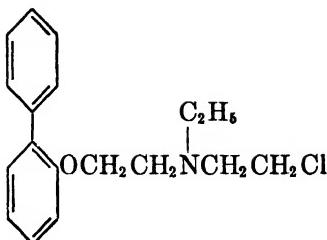
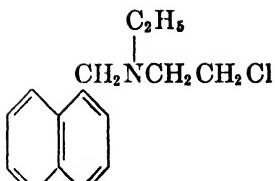
Several American publications appeared shortly thereafter. In 1945 Loew (263) reported tests on a series of benzhydryl alkamine ethers which had been synthesized by Rieveschl and Huber (367). 2-Dimethylaminoethyl benzhydryl ether (Benadryl) and several related tertiary amines were found to exert definite antihistaminic and antianaphylactic action.

Also in 1945 Mayer (277, 278) reported the considerable activity of *N*-(α -pyridyl)-*N*-benzyl-*N'*,*N'*-dimethylethylenediamine (Pyribenzamine). Benadryl and Pyribenzamine were immediately and widely used by the medical profession, and many pharmacological and clinical reports on their use have been published.

A multitude of compounds have been prepared and tested for antihistaminic potency. In many cases, patents and publications are extremely vague as to the latter. The structures and activity of all synthetic antihistamines will be noted in the subsequent portions of this paper.

About twenty compounds have been offered for clinical use (195). Table 1 lists these and recently published active compounds in alphabetical order. Their syntheses and properties will appear in the main body of the review.

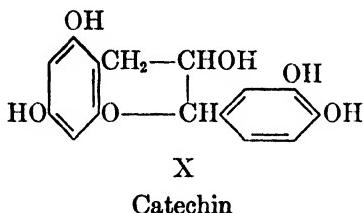
Aryl-substituted β -haloalkylamines have been demonstrated to be potent antihistaminics; in contrast to other agents which enhance the pressor action of epinephrine, these compounds block and reverse this pressor action (257). *N*-2-Chloroethyl-*N*-ethyl-1-naphthalenemethylamine (VIII) and 2-(2-biphenylyloxy)-2'-chlorotriethylamine (IX) exert this dual action. Chemically, these compounds are related (177) to Dibenamine [*N*-(2-chloroethyl)-dibenzylamine], a compound which exerts adrenergic blocking action but which is almost devoid of antihistamine action (302, 303, 305). Nickerson (301) has covered the pharmacology of "adrenergic blockade" in an excellent review. The principal clinical



application of these drugs appears to be in the group of peripheral vascular diseases.

The adrenocorticotropic hormone (ACTH) has been used with remarkable success in treatment of the allergic reactions of asthma, hay fever, and drug sensitivity (149a). This work was based on the experimental studies of Rich and Gregory (346, 347), which suggested a relationship between the hypersensitive state and rheumatic diseases.

Based upon the hypothesis that greater therapeutic value would result from the prevention of the formation of histamine than from prevention of its action, as occurs with standard antihistamines, studies were made of the inhibition of histidine decarboxylase, an enzyme in animal tissues which is capable of forming histamine from histidine. Flavonoids proved to be the most effective inhibitors. Catechin (X) protected guinea pigs against anaphylactic shock, but not from



histamine shock (296). The results were interpreted as reflecting *in vivo* inhibition of histidine decarboxylase.

III. TESTING

A. PHARMACOLOGICAL

Antihistaminic drugs are assayed by observing whether or not they will inhibit or block one or more of the easily demonstrable pharmacological effects of histamine. In one test, the lethal dose of histamine injected intravenously is determined for a group of guinea pigs. The compound to be tested is injected subcutaneously and increasing doses of histamine are thereafter given to determine the maximum dose which the animal survives and thus the protective effect of the drug. A second test is designed to measure the protective action of

the drug against the lethal effect of histamine inhaled by a guinea pig. If the animal is subjected to a fine mist of histamine solution, respiratory distress occurs within a short time. On removal from the spray the animal will recover, but if it is allowed to remain exposed to histamine, death will occur from asphyxiation due to a muscular spasm of the bronchioles, which prevents sufficient ventilation of the lungs. Guinea pigs that have received a sufficiently large oral or parenteral dose of an antihistaminic are able to resist the asphyxial action of histamine for much longer times. The dose of the drug that is necessary for this protective effect is a measure of its antihistaminic potency. Since protected animals can be exposed repeatedly to the histamine spray at regular time intervals, the return of the asphyxial signs may be observed as the drug is eliminated by the animal; thus a measure of the duration of activity may be obtained. The third general test determines the power of the antihistamine to prevent contraction of the isolated ileum of the guinea pig. By appropriate adjustment of the concentrations of histamine and the antagonist, an assay method is devised whereby one antihistaminic may be compared with another. The estimate of activity is derived from the ratio of the concentrations of the antihistamines that cause equal inhibition of the histamine spasm. A fourth test determines the effect of a drug in preventing the depressor action of histamine on the blood pressure of a dog or cat. The final major test measures the capacity of the antihistaminic to abolish or diminish the size of a wheal caused by an intradermal injection of histamine (344).

Other more precise methods have been developed, including the use of the tracheal chain (66, 67, 68), canine spinal fluid pressure (390), and area changes in the bronchi of dogs and cats (132). An equation relating the affinity of histamine and the antihistamine for the cell receptor has been proposed (449). Precise results were obtained (289, 381, 382), utilizing an older idea (91) of measuring drug antagonism through the concentration which would neutralize the effects of a tenfold increase of the drug. The dynamics of recovery for the isolated intestinal strip was considered a reliable quantitative assay (21, 370). Antihistaminic activity can be measured *in vivo* by means of fluorescein (50). In *normal* subjects fluorescein disappears rapidly under the influence of histamine, and antihistaminic substances always neutralize this effect. In *allergic* subjects fluorescein alone is visible only for a short time, but when antihistaminics are added fluorescence is visible for a prolonged period of time. Avoidance of large standard errors of group assays is proposed through the equations of S. Loewe (266, 267), while time-per cent curves give rapid nomographic solutions (255). The inhibition of the spasmogenic effect of histamine or acetylcholine following a short exposure is used as a differentiation of the two innervators (174, 271). Histamine iontophoresis has been used to determine comparative activity in man. The initial threshold is determined by the highest dilution of histamine base producing diffuse punctate whealing. The threshold of the drug is redetermined by administering it orally and the difference between the two determinations is a measure of activity (412).

B. CHEMICAL

1. Histamine

The normal histamine content of human blood as determined by bioassay ranges from 1 to 8 gammas (γ) per 100 ml., with an average value of about 4 γ (186, 371). These low levels have limited the development of chemical analysis until suitable micro methods could be developed.

Two chemical methods which have become available for the analysis of histamine in biological fluids involve the coupling of imidazoles with 4-nitroaniline (378, 419) and with 2,4-dinitrofluorobenzene (280, 281). The two methods were combined and modified (269) to permit the colorimetric analysis of 0.1–1.0 γ of histamine in a 5–10 ml. specimen of whole blood. Chromatography has been successfully applied to the problem (437). Sodium 1,2-naphthoquinone-4-sulfonate (270) and *p*-bromoaniline (20, 436, 437, 438) have been recommended as colorimetric reagents.

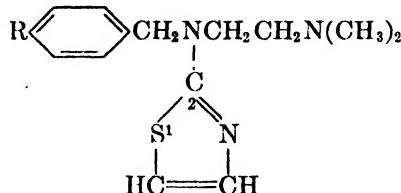
2. Antihistamines

Specifications and identifying tests for Benadryl (298), Pyribenzamine (337), Thenylene (334), Neohetramine (336), Decapryn (333), Trimeton (335), Dramamine (297), and Antistine (332) have been reported in *New and Non-Official Remedies*. The tests described are nonspecific.

Haley and Keenan (168, 171, 172, 173, 174, 221) studied the reactivity of several antihistaminic drugs with simple alkaloidal precipitants and color reactions to see if such tests could serve as means of identification. Benadryl and Pyribenzamine gave the same type of precipitate with most of the precipitation reagents. The only reagent useful in their identification was chloroplatinic acid (168, 221), with which different crystalline precipitates were obtained. The results of precipitation and colorimetric tests on several different antihistaminic drugs brought forth many distinctive differentiations and identifications (table 2).

Crystallographic properties, also determined by Haley and Keenan, pointed out even better means of identification. Excellent photomicrographs were obtained, using the immersion method with the polarizing microscope (171, 172, 173).

The effect of radical substitution on the optical properties of derivatives of *N*-2-thiazoleethylenediamine (White 194B; table 1, No. 27)



where R represented hydrogen, chlorine, or methoxy, yielded interesting observations (222). The crystal habits of the three substances appeared essentially

identical in ordinary light. However, there was a very marked difference in the axial angles. The angle was quite large where hydrogen substitution occurred and was much smaller when chlorine was in position. Cavallini recorded the effect of various alkaloidal reagents on benzhydryl 2-imidazolin-2-ylmethyl ether (71).

The analytical method of Brodie (43, 44, 45, 46, 47) for the analysis of organic bases was utilized for the determination of the changes in concentration of Benadryl and Pyribenzamine in blood, urine, and spinal fluid (160). The method depends on the reaction of the organic base with methyl orange to form a colored complex salt which is soluble in ethylene dichloride. Dill (111) noted that the above procedure gave high blanks in the analysis of urine and tissues and therefore utilized a double-extraction technique to eliminate interferences. The identity of Benadryl in the urine was established by counter-current extraction with the Craig technique (96) and by the ultraviolet absorption spectrum (162a).

The red color with concentrated sulfuric acid gave a sensitivity of 20 mg./l. of Neoantergan (117). The turbidity of an ether extract of a protein-free blood filtrate after treatment with iodine allowed measurement of 5 γ of Pyribenzamine and 3 γ of Antistine per milliliter of human blood (321).

A colorimetric method for the determination of *N*-(2-pyridyl)-substituted antihistamine drugs consists in the opening of the pyridine ring by cyanogen bromide and the coupling of the intermediate compound with aniline, resulting in the formation of a yellow complex which follows Beer's law (213, 316). Ammonium reineckate, in aqueous solution, quantitatively precipitated most of the antihistamine compounds. The precipitates are isolated, dissolved in acetone, and determined colorimetrically (17). Various sympathomimetic amines, such as ephedrine, amphetamine, and desoxyephedrine, did not interfere.

The ultraviolet absorption spectra of a large series of antihistaminic compounds were determined (148, 149) to ascertain whether adequate sun screening could be obtained. Characteristic spectra with well-defined maxima were found for *N*-(2-pyridyl)ethylenediamines and form the basis for excellent determinations (9, 88, 273). Four micrograms of Thenylene or Neoantergan was determined with an accuracy of ±0.5 per cent.

Compounds containing nitrogen, sulfur, and halogens may be analyzed, after combustion, by standard methods. The bases can be titrated with standard acid and the acid salts with standard alkali, but these methods are nonspecific.

IV. HISTAMINE ANTAGONISTS

Bovet and Bovet-Nitti (32), in their book on drugs affecting the autonomic nervous system, classify antihistaminic agents according to their mode and site of action. The compounds are separated into two groups, dependent on whether their pharmacological action resembles that of sympathomimetic and sympatholytic agents or whether their antagonism is mainly directed toward the parasympathetic nervous system. In the first group are placed the phenolic ethers and derivatives of aniline, α-aminopyridine, aminopyrimidine, phenylamino-methylimidazoline, aminochloroethane, and phenyltetrahydropyridindene. In

the latter spasmolytic grouping are placed the benzhydryl ethers, derivatives of phenothiazine, and esters of phenyl- α -thenylglycolic acid.

This review will not utilize a pharmacological division, but will employ a broader structural classification, dividing the histamine antagonists into derivatives of ethanolamine, derivatives of ethylenediamine, derivatives of amino-propane, derivatives of phenyltetrahydropyridindene, and amino esters.

A. DERIVATIVES OF ETHANOLAMINE

1. *Phenolic ethers*

2-Thymyloxytriethylamine (IV) was the first synthetic substance which was found to exhibit potent antihistaminic properties (38). The weak sympatholytic properties of the compound had been noted previously (7, 8). Staub described (407) the antihistaminic properties of the phenoxyethylamines prepared by Maderni (36) (table 3).

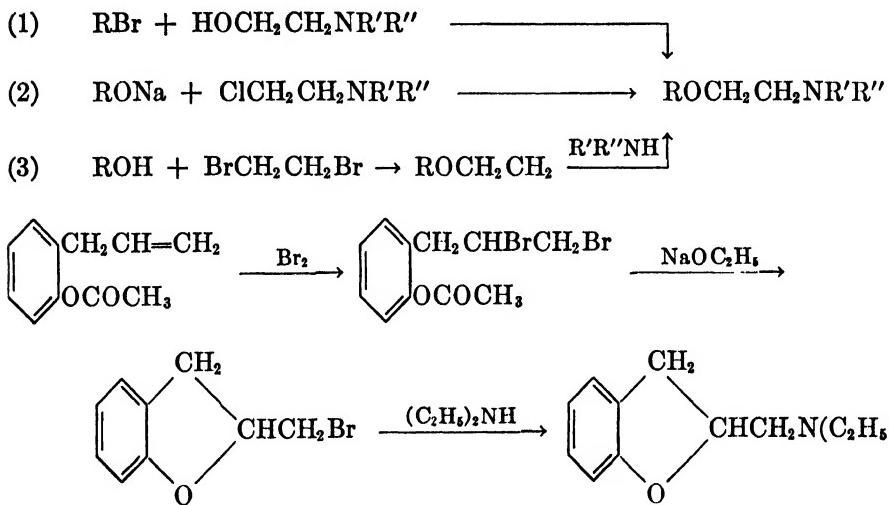
Various relationships between chemical constitution and antihistaminic activity were observed. The nitrogen atom in the alkyl side chain must be tertiary, for replacement of one of the ethyl groups in the amine radical, to yield the secondary amine (F 1482), suppressed all activity. Replacement of the diethylamino group by piperidine (F 1462) caused a large decrease in activity. Isomeric compounds had practically identical actions (F 929 and F 1379; F 1482 and F 1483; F 1464 and F 1465). Of the various derivatives of (2-phenoxyethyl)-diethylamine or F 928 (F 940, F 1274, F 1262, F 1306, F 1323, F 1655), only 2-(2-biphenyloxy)triethylamine (F 1262) possessed activity, but its cardiac activity precluded any further study. Tastromine, the dimethyl analog of F 929, is probably slightly superior to the latter, but its histaminolytic properties have not been fully investigated.

Monobasic and polybasic aryl ethers, prepared and studied by Protiva (327), exhibited very mild activity (table 4, Nos. 1-13). The ortho-disubstituted phenol possessed 10-30 times the activity of the meta- and para-substituted (Nos. 2 and 3) and the trisubstituted ethers (Nos. 4 and 5). The aminoalkyl benzyl and benzhydryl ethers (Nos. 6-9) were appreciably more active, while the benzhydryl thioethers (Nos. 12 and 13) were of the same order of activity, with diminished toxicity (No. 13). The diphenyl derivatives (Nos. 11 and 12) are relatively inactive, compared to the benzhydryl ether derivatives (table 5) and the recent potent derivatives of benzylphenol (table 19).

Dialkylaminoalkyl thioethers were prepared to study the effect of replacement of oxygen and nitrogen in compounds of the type of Benadryl and Pyribenzamine (table 4, Nos. 14-21) (31). The pharmacological properties were not reported.

The amino ethers were prepared either by the condensation of the aryl bromide with a dialkylamino alcohol, or by that of the sodium salt of the cyclic alcohol with a dialkylaminoalkyl halide. A variation of the latter method consists in reacting the cyclic alcohol with ethylene bromide and treating the resultant

bromo ether with a dialkylamine. F 929 was initially synthesized by the vacuum distillation of β -diethylaminoethylthymyl carbonate (124, 125). Fourneau and Lestrange (*cf.* 407) heated sodium thymolate in a sealed tube with 2-chlorotriethylamine. The same result has been obtained in open reflux (106). Thymoxyethyl bromide (from thymol and ethylene dibromide) and diethylamine give the desired product (373). F 883 (II) was obtained from the condensation of catechol and epichlorhydrin in the presence of alkali and reaction of the product with dimethylamine (145). The ring closure of the substituted allylphenol yielded the corresponding coumaran. The benzodioxan was relatively inactive, protecting only 30 per cent of test animals from a single toxic dose of histamine (433).



The dialkylaminoalkyl aryl ethers and thioethers (table 4) resulted from the condensation of sodium phenates and thiophenates with chloroalkylamines (31, 327).

2. Benzydryl ethers

The ethers of benzydryl represent the first potent histamine-antagonizing drugs which originated in the United States. The most active of an initial series of seventeen benzydryl ethers tested by Loew, Kaiser, and Moore (263) (table 5) was the dimethylaminoethyl derivative, Benadryl (table 1, No. 3), synthesized by Rieveschl and Huber (354, 367), which protected guinea pigs against seventy-



XII

Trasentin

five toxic doses of histamine. The benzhydryl ethers are closely related to the spasmolytic agents and the acetylcholine antagonists of the Trasentin (XII) type, which are benzhydryl esters. Loew (264) compared the antispasmodic and antihistaminic activity of atropine, papaverine, Trasentin, Pavatrine, Benadryl, and F 1571. Benadryl was a much more potent antispasmodic than Pavatrine and Trasentin, the most effective antispasmodics. It exerted weak antagonism against barium, and moderate antagonism against acetylcholine, the latter being one-half to one-tenth that exhibited by Trasentin and Pavatrine. F 1571 (V) was comparatively impotent in antagonizing barium and acetylcholine.

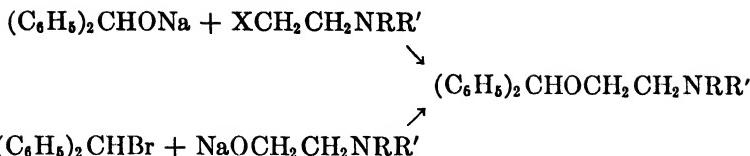
The three most potent compounds in table 5, listed therein in descending order of activity, were the 2-dimethylaminoethyl, 2-piperidinoethyl, and 2-morpholinoethyl benzhydryl ethers. The first two are at least twice as potent as benzhydryl 2-morpholinoethyl ether, which has an activity comparable to that of F 1571, the most active Fourneau antagonist.

Several conclusions can be drawn concerning the relationship between molecular structure and antihistamine activity (263). A chain length of two carbon atoms is found in the five most active compounds (table 5, Nos. 1-5). Compounds with longer or branched carbon chains are less active. This is apparent in comparing No. 3 with Nos. 8, 12, and 14; however, the relative potency of Nos. 6 and 7 opposes this view. An increase in chain length obtained by an oxygen-interrupted chain (No. 15) also decreased the activity. The character of the substitution on the nitrogen atom is seen by comparing Nos. 1, 4, and 9, in which the activity is in the order of the tertiary > secondary > primary amine. In general, the data indicate that an increase in the size of the group on the nitrogen atom leads to less active compounds in both the secondary and the tertiary amines (compare Nos. 4, 5, and 13; also Nos. 1, 6, 16, and 17). No. 11 represents one example of substitution on the benzene rings of the benzhydryl group. On comparison with the analogous unsubstituted compound (No. 3) the 4,4'-dichlorobenzhydryl 2-morpholinoethyl ether is seen to be much less active, but also less toxic. Substitution in the benzhydryl part of Benadryl resulted in major loss of activity. Simple substitution of halogen, or rearrangement of phenyl rings to give fluorene or naphthalene derivatives, resulted in agents with little activity. Lesser toxicity was claimed for the *p*-methoxy derivatives (159).

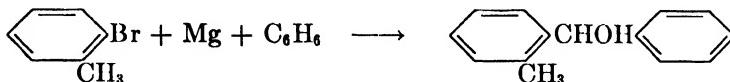
Rieveschl, in a series of patents (349, 350, 351, 352, 353, 354, 355, 356, 358, 366, 367), has described an extensive series of benzhydryl ethers prepared by the condensation of a benzhydryl halide with the appropriate dialkylamino alcohol, usually in the presence of an acid-binding agent, such as an alkali carbonate.



Alternate methods of preparation included the reaction of an alkali metal salt of benzhydrol with a 2-dialkylaminoethyl halide or the reverse condensation of the alkali metal salt of a 2-dialkylaminoethanol with a benzhydryl halide.



Substituted benzhydrols have been made *via* the Grignard addition compound (326).



Benzhydryl bromide was obtained when diphenylmethane and bromine were heated together, with illumination (354). The benzhydrols are readily obtained by the reduction of the benzophenone with either aluminum isopropoxide or zinc dust and alcoholic caustic (165). The ethers of the 1-alkyl-4-piperidinols were obtained from either the benzhydryl halide and the piperidinol or the 1-alkyl-4-halopiperidine with the alkali salts of benzhydrol (226).

Table 6 lists reported benzhydryl ethers according to structural similarities. Methods of synthesis are not reported, since practically all preparations are performed as previously described.

A number of benzhydryl sulfones, synthesized by Klenk and Suter (225), have been tested as analgesics.

The studies of Alles and Redemann (6) on the comparative spasmolytic activities of the salts of Nos. 6, 7, 8, 12, 13, 14, 15, and 73 (of table 6) are shown in table 6A. Examination of the results of table 6A shows that single or double branching of the chain with a methyl group, in either the 1- or the 2-position of the ethyl group in benzhydryl dimethylaminoethyl ether, diminishes the anti-histamine activity. This diminution can also be viewed in the light of changing the oxygen function of the α -carbon of the alkyl part of the ether from that of a primary carbinol to that of a secondary and tertiary carbinol, and of changing the nitrogen function of the β -carbon of the alkyl part of the ether from that of a primary carbidiomethylamine to that of a secondary and tertiary carbidiomethylamine.

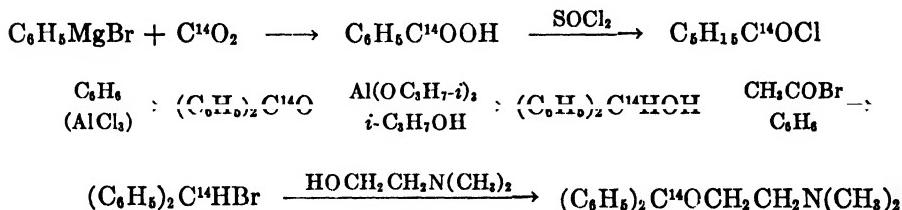
The lengthening of the alkyl group of the ether from that of a 2-dimethylaminoethyl ether to a 3-dimethylaminopropyl ether also diminishes the antihistamine activity. The introduction of a triphenylmethyl radical rather than the diphenylmethyl radical, with the increase in the electronegative character of the carbon adjacent to the ether link, diminished activity, though this may also (and more probably) be related to the very considerable concomitant increase in the size of the molecule.

A comparison of the *m*-chloro derivative of Benadryl (table 6, No. 63) with Benadryl revealed it to be three times as active and less toxic (290).

Wright, Koloff, and Hunter (463) prepared two alkamine ethers (table 6, Nos. 20 and 29) by the reaction of the disubstituted methyl bromide with the

requisite amino alcohol in the presence of anhydrous potassium carbonate. The hydrochloride of benzhydryl 2-pyrrolidylethyl ether (No. 20) possessed 1.5-2 times the activity of Benadryl, while that of benzhydryl 2-(4-methylpiperazyl) ethyl ether had only 0.1 the activity.

To aid in metabolic studies (163), Fleming and Rieveschl (139) prepared Benadryl containing isotopic C¹⁴. The C¹⁴O₂ was generated from barium carbonate containing 6.88 mc. of C¹⁴. The overall yield based on barium carbonate was 55 per cent.



To offset the drowsiness caused by certain antihistamines, attempts were made to combine the bases with the methylxanthines, selected because of their stimulation of the central nervous system. Because of the low ionization constants of the methylxanthines, however, no stable salts were obtained. The problem was solved by the use of 8-chlorotheophylline, which has a high enough ionization constant to form a stable salt (100). Dramamine (table 1, No. 10), the 8-chlorotheophylline salt of Benadryl, has received wide publicity in the treatment of motion sickness. Its antihistaminic potency and spasmolytic activity are respectively 1.5 and <1 times that of the ether on a molar basis (158). Cusic (101) prepared various xanthine salts of 2-dimethylaminoethyl ether by the action of a haloxanthine on a diarylalkyl ether of an amino alcohol (table 7).

3. Quaternary ammonium salts of benzhydryl alkamine ethers

Conversion of the tertiary amines derived from benzhydryl ethers to quaternary ammonium salts does not alter the antihistaminic action to a great degree, but greater antispasmodic qualities become evident. The methiodide of Benadryl [(2-benzhydryloxyethyl)trimethylammonium iodide] was approximately one-half as effective as Benadryl against histamine and barium, but four times more potent with respect to the antagonism of acetylcholine action, on intestinal muscle (264). Thus, atropine-like qualities were increased at the expense of antihistamine properties. Winder, Kaiser, Anderson, and Glassco (459) present an excellent discussion of the resultant of the influences of molecular structure at both ends of two carbon alkylamine bridges, which are of primary importance in the physiology and pharmacology of the autonomic nervous system (32). In the adrenergic system an optimal circumstance of the aminoethyl chain appears to be extension or attachment to the aryl structure; in the histaminic system, attachment to a heterocyclic structure for activation or through an ether or nitrogen linkage to an aryl or aralkyl group for interference; in the cholinergic

system, either ester or ether linkage, with quality and quantity of action influenced by the state of both molecular extremities. In the structure of Benadryl, as compared with that of histamine (I), the 2-imidazolyl structure of the latter is replaced by a benzhydryl ether group, and as the function of the nitrogen is changed from primary to tertiary the histamine interference increases (263). Thus, in the presence of the benzhydryl ether group, as histamine interference increases, the function of the nitrogen progressively deviates from that in histamine. From this view it is not surprising to find essential maintenance of interfering potency in passing on to the quaternary amines. These are now in the class of choline derivatives, in the cholinergic system (459). Ing (205) found that atropine-like action was sharply increased by substituting ethyl for one of the three *N*-methyl groups of the benzilic acid esters of quaternary ethanolamines. The presence of the quaternary function is associated with curariform, parasympathomimetic, nicotinic, and adrenergic activities (204).

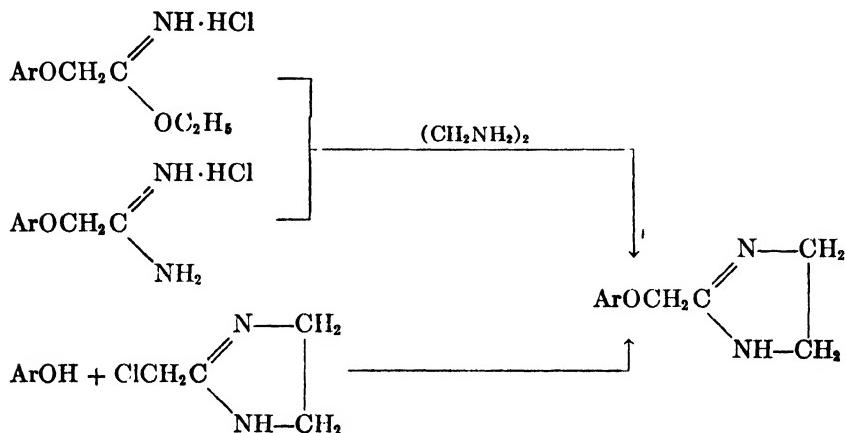
Table 8 lists some quaternary salts of benzhydryl ethers which were synthesized by treating the substituted aminoalkyl or chloroalkyl benzhydryl ether with the appropriate alkyl halide or alkylamine (351). The methiodide (No. 3), methochloride (No. 1), methyl *p*-toluenesulfonate (No. 5), and methosulfate (No. 4) were the most active of a series of quaternary salts initially tested (262). The failure of the present compounds to show any remarkable difference in histamine-interfering potency suggests that the ionic state is not of the order of importance that it is in the cholinergic system. The quaternary compounds do not appear promising as visceral spasmolytics because of a lack of good myotropic action to accompany the atropine-like action (458). There is a suggestion of increased toxicity in the ethyldimethylammonium derivatives (Nos. 6, 7, 8, and 9). This may be due to the approach to the curariform action of the triethylammonium ethers. A series of quaternary benzhydryl ethers have been patented for this activity (359), while long-chain molecules have been advanced as germicides (365).

4. Aryloxyimidazolines and amidines

The desirable features of 2-(*N*-benzyl-*N*-phenylaminomethyl)-2-imidazoline (Antistine, table 1, No. 2) prompted substitution searches in the ether series. In addition to their antihistaminic action, the imidazoline agents appear to have some direct effect upon almost every organ of the body. These effects are highly varied. This lack of specificity is not surprising, since only slight changes in the structure of Antistine produce the sympathomimetic drugs Privine [2-(1-naphthylmethyl)-2-imidazoline] and Otrivine [2-(anilinomethyl)-2-imidazoline] (301). Djerassi and Scholz (113, 115, 365) noted the similarity in the side chain of Antistine to that of Antergan (VII), 2-methylimidazolyl replacing the dimethylaminomethyl moiety. Since this change enhanced the desirable activity, the observation was extended to variations of the side chain of ring-alkylated aryl-oxethyldialkylamines, of which F 929 (IV) is the best-known example. Since imidazolines can be considered to be cyclized amidines, aryloxyacetamidines were added to the investigation of the 2-(aryloxymethyl)imidazolines (113).

The amidines (table 9) were prepared by condensing ring-acylated phenols with chloroacetonitrile by a modification of the conventional Claisen *O*-alkylation of phenols. Treatment with ethanolic hydrochloric acid gave the ethyl aryloxyacetimidate hydrochlorides, from which the desired amidines were obtained with ammonia or substituted amines.

The aryloxymethylimidazolines (table 10) were synthesized by three different methods. The method of choice was the condensation of the imidic ester hydro-

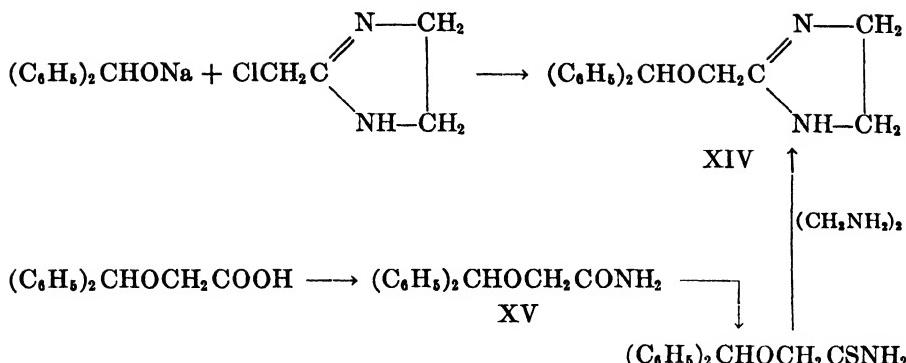


chloride (XI) with ethylenediamine (401).

Inspection of the pharmacological results (201) reveals that all the phenoxy compounds (table 9) were relatively inactive; this confirms Staub's rule to the effect that in the ether series the ring should be substituted. The 2-(thymyl-oxymethyl)-2-imidazoline was found to be at least as effective as F 929 (407), indicating that in this series the 2-imidazolylmethyl group was equal or superior to the diethylaminoethyl side chain. Most of the imidazolines were strong vaso-pressors with the exception of the 2-(*p*-cresoxymethyl)-2-imidazoline (table 10, No. 27), which showed adrenolytic action.

The analogy approach was applied to 2-dimethylaminoethyl benzhydryl ether (114). 2-(Benzhydryloxyethyl)-2-imidazoline (XIV) was synthesized and found to be a strong histamine antagonist (170). The same compound was prepared almost simultaneously in other laboratories (70, 71, 104, 328). The compound could be made either by the direct condensation of sodium benzhydrolate and 2-(chloromethyl)-2-imidazoline hydrochloride in toluene suspension (224) or by the conversion of benzhydryloxyacetamide (XV) to the thioamide, which reacted with ethylenediamine to afford the desired imidazoline (XIV).

All the various imidazoline derivatives subsequently prepared were made by either of these procedures. Reduction of 2-benzoylthiophene with aluminum isopropoxide gave 2-thienylphenylcarbinol, which was condensed with 2-(chloromethyl)-2-imidazoline, in the presence of sodium amide, to give 2-(thienylphenyl-oxymethyl)-2-imidazoline (cf. *p*-methoxyphenyl derivative: table 11, No. 15).



The pyridylmethylcarbinol (table 11, No. 16) resulted from a similar procedure (103). The compounds possessed only weak antihistamine action.

2-(Benzhydryloxymethyl)-2-imidazoline was about one-half as toxic as Pyribenzamine (table 1, No. 19) in rats and demonstrated antihistaminic and antianaphylactic properties comparable to those of Benadryl and Pyribenzamine. In contrast to most antihistaminic drugs, this substance relaxes the bronchiolar muscles of the guinea pig (114). Table 11 gives a list of aryloxyalkylimidazolines other than those initially prepared by Djerassi and Scholz (114).

5. Dioxolanes

Certain 1,3-dioxolanes have exhibited a high degree of spasmolytic activity. Brown and Werner (48) studied the parasympathetic depressant and antihistamine action of certain substituted 1,3-dioxolanes prepared by Blicke and Anderson (27) and by Blicke and Schumann (*cf.* 48) (table 12). The antihistamine activity was generally weak for all compounds; however, No. 10 had activity similar to that of certain antihistamines used clinically, while No. 5 was a potent parasympathetic depressant. The change to quaternary ammonium salts from halogen acid salts generally resulted in increased antiacetylcholine activity.

6. Heterocyclic substituted alkamine ethers

The extremely favorable change in therapeutic index which resulted from the replacement of the phenyl group in the Fourneau ethers (table 3) by the benzhydryl group (tables 5 and 6) prompted various investigators to substitute heterocyclic groups for phenyl in the benzhydryl portion.

The effect of heterocyclic replacement of one or both of the aryl functions (tables 13, 14, 15, 16, and 17) resulted in extreme limits of variation in toxicity and potency. The 1-pyrrolidyl and 4-methylpiperazyl benzhydryl ethers were appreciably more active (table 6, Nos. 20 and 30) than Benadryl. They were synthesized by treatment of the sodium (lithium) salt of the appropriate disubstituted carbinol with the aminoalkyl chloride.

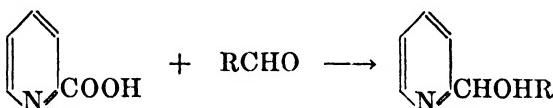


The use of one equivalent of 2-dimethylaminoethyl chloride resulted in low yields. This may be attributed to the ease with which the halide forms a cyclic piperazinium salt. The use of a large excess of the chloride did not materially improve the yield. Satisfactory results were obtained by treatment of the disubstituted carbinol with one equivalent of sodium or lithium amide to liberate the dimethylaminoethyl chloride from its salt.

A number of substituted dialkylaminoalkyl pyridylalkyl ethers were synthesized by Schwenk and coworkers (table 14) (405). The most active compounds were the 2-pyridyl derivatives in which R' is phenyl or an alkoxy, alkyl, halogen, or dimethylamino substituted phenyl group, R'' is hydrogen or a methyl group, and R''' is methyl. These compounds (Nos. 1, 3, 4, 5, 6, 7, 10, 19, and 20), referred to as group 1, exhibited antihistaminic activity comparable to that of Benadryl. The oral L.D.50 in mice was approximately 300–400 mg./kg.

Lower antihistaminic activity is exhibited by the 3-pyridyl compounds (Nos. 2, 8, and 21) and the 2-pyridyl compounds wherein R' is 3,4-methylenedioxyphenyl (No. 8), benzyl (No. 11), phenethyl (No. 12), 2-thienyl (No. 13), *n*-propyl (No. 14); or wherein R''' is C₂H₅ (Nos. 15 and 16). Variations in the length of the carbon chain of the ether also result in decreased potency (No. 17). In general, these compounds possess 1/5 to 1/100 the activity of the compounds in group 1.

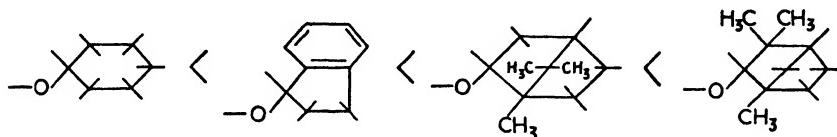
The pyridyl-substituted alkamine ethers were synthesized by the condensation of the appropriately substituted carbinols with dialkylaminoalkyl halides and sodium amide in toluene. The yields varied from 45 to 88 per cent. The secondary substituted 2-pyridylcarbinols were made by the decarboxylation of picolinic acid in the presence of an aromatic aldehyde at a temperature above 140°C. The products of the reaction are the desired carbinol, pyridine, and carbon dioxide.



A large group of similar basically substituted pyridine derivatives was synthesized by Tilford, Shelton, and Van Campen (423, 424, 425) (table 15). The antihistaminic activities showed that Nos. 1 and 7 were the most active of these tested. Substitution on the phenyl group of either of these compounds with alkyl, alkoxy, or halogen groups does not increase the activity, although Nos. 7, 9, 16, 17, 19, 20, and 21 have about equal potency. When a naphthyl (Nos. 14 and 15), pyridyl (No. 33), thienyl (No. 34), or cyclohexyl (No. 28) group replaced the phenyl group of No. 7, the activity was diminished considerably. The greater the degree of hydrogenation of the R group of No. 7, the lower the activity (No. 28 < No. 27 < No. 7). Replacement of the pyridine ring with a piperidine group has no apparent beneficial antihistaminic effect, as shown by the low order of activity of Nos. 53 and 54.

As the length of the carbon chain of group R' increased beyond one carbon

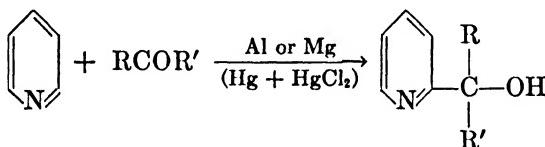
atom, the potency decreased: thus No. 23 < No. 22 < No. 7. Substitution on the chain with basic groups (Nos. 24 and 32) also lowered the activity. The antihistaminic effect of cyclic compounds (group B in table 15) seems to increase with branching on the carbon atoms near the ether linkage.



Compounds of group C (table 15), in which the point of attachment to the pyridine ring is at the 3- or 4-position, are not within the range of potency of Nos. 1 and 7. An additional methylene group separating the phenyl or the pyridyl ring from the ether linkage is detrimental to the antihistaminic activity, as shown by Nos. 8 and 42. Any variation of the dimethylaminoethyl side chain of No. 7 decreases the potency.

The most active compounds (Nos. 1, 7, and 9), when administered intravenously to guinea pigs at levels of 4-32 mg./kg., gave complete protection against 50-300 fatal doses of histamine injected intravenously.

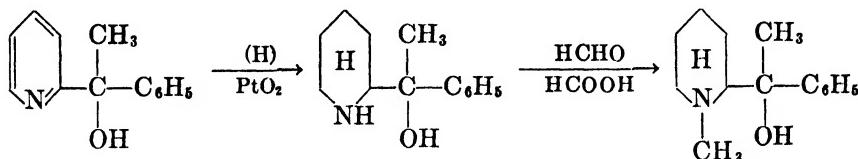
The most convenient method for the preparation of the α -substituted pyridinemethanols was through the condensation of a ketone with pyridine in the presence of aluminum or magnesium, mercuric chloride, and iodine.



Magnesium was a superior agent for condensing benzaldehyde with pyridine, whereas with substituted benzaldehydes the yields with aluminum were about the same as those with magnesium.

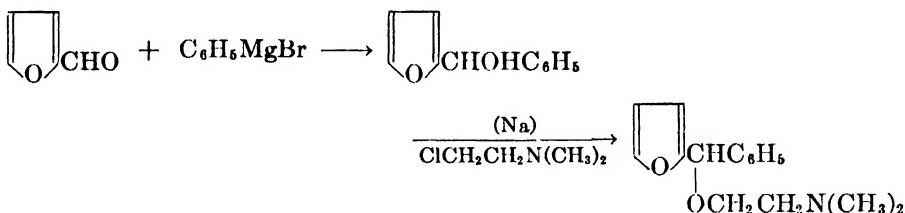
Preparation of these types of carbinols have been reported, using either pyridylmagnesium bromide (308, 325) or picolinic acid (11) and the carbonyl compound, as well as phenylmagnesium bromide and a pyridylcarbonyl derivative (430). A 3-pyridinemethanol (232) resulted from the reaction of 3-pyridylmagnesium bromide and benzaldehyde.

Several of the pyridinemethanol hydrochlorides were reduced catalytically to the piperidinemethanols. A compound where R is methyl (table 15, No. 54) was treated with formalin and formic acid and the N-methyl derivative was obtained.



The synthesis of 2-pyridinemethanol has recently been simplified (123). 2-Picoline was converted to the lithium salt by the hydrogen–metal interchange reaction between 2-picoline and phenyllithium. The picollyllithium was oxidized with a slow current of air to form the 2-pyridinemethanol. The effectiveness of Decapryl (table 1, No. 8; table 15, No. 7) as an antihistaminic agent prompted the preparation of the 2-pyrimidine- and 2-imidazoline-methanols (425) and their dimethylaminoethyl ethers (table 16, Nos. 1 and 2) (425), which were about 0.0025 as active as Decapryl.

The furyl isostere of Benadryl (table 16, No. 3) was prepared from furfural and the phenyl Grignard reagent (25).



This phenyl-2-furylmethyl 2-dimethylaminoethyl ether proved to be less than twice as active as Benadryl.

2-Diethylaminopropyl sulfides were prepared in an attempt to synthesize sulfur compounds analogous to Benadryl and Pyribenzamine with sulfur replacing the oxygen and the nitrogen linkage, respectively. The general structure of the molecule differs from these antihistamine drugs in that only one aryl group is present instead of the diaryl groups (table 17).

The 3-diethylaminopropyl derivatives were prepared by condensing the potassium arylthiolate with 3-diethylaminopropyl chloride. The derivatives of 1-diethylamino-2-propanol were prepared from the sodium salt of the aryl mercaptan with 1-diethylamino-2,3-epoxypropane. No pharmacological data were presented (31).

A large variety of *N*-2-pyridylalkanolamines were prepared by Weiner and Kaye (448) by heating 2-bromopyridine with the appropriate amino alcohol. Moffett (291) synthesized a series of pyrrolidylalkanols by a variety of methods. Lithium aluminum hydride was found to be very satisfactory for the reduction of pyrrolidyl-substituted esters or ketones to pyrrolidyl alcohols, and for the reduction of substituted pyrrolidones and succinimides to pyrrolidines.

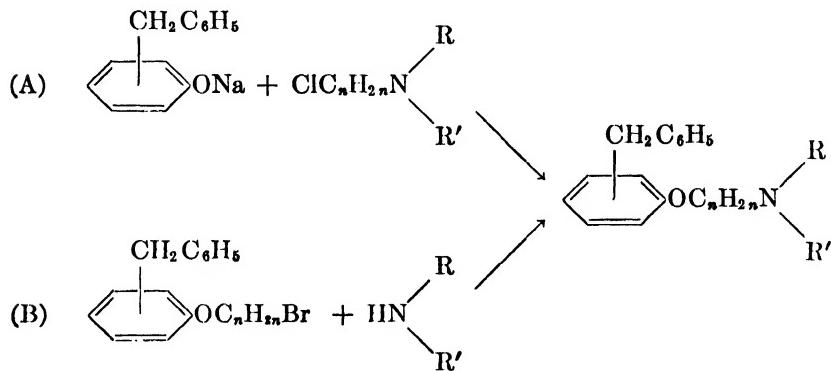
Heterocyclic ethers were prepared as part of a larger study by Sutherland and coworkers (415) (table 18), by modifications of the Williamson ether synthesis. Each of the dimethylaminoethoxy compounds was made by dissolving sodium metal in an excess of dimethylaminoethanol and then treating with the appropriate aromatic halide. None of the compounds was more active than Benadryl.

7. Benzylphenols

The effectiveness of F 929 (IV) and Benadryl (table 1, No. 3) led Binkley and coworkers (81, 453, 454, 456) to investigate the effect of the substitution of the benzyl group in the phenolic ethers (table 19). The hydrochloride of 2-benzyl-

phenyl 2-dimethylaminoethyl ether (C-5581-H, No. 4 in table 1) proved relatively nontoxic and elicited the highest order of antihistaminic and local anesthetic activity in animals. In contrast, the isomeric 4-benzyl (338-20) compound exhibited a low order of antihistaminic action. In general, branching or lengthening the alkylene chain, $\text{—C}_n\text{H}_{2n}\text{—}$, or replacing the dimethylamino group with other secondary amines did not lead to increased potency.

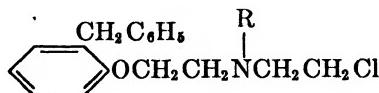
With the exception of the two hydrogenated derivatives (489-1 and 489-2), all of the compounds in table 19 were prepared by condensing sodium benzylphenoxide with the appropriate aminoalkyl chloride (A). Where low yields resulted, an ω -bromoalkyl ether of a benzylphenol was reacted with the appropriate amine (B). This proved to be the procedure of choice for the synthesis of an ether bearing a secondary amino group. Owing to the tendency for free alkylaminoalkyl chlorides to polymerize when heated in the presence of polar solvents, toluene was employed as a reaction medium and sodium or sodium hydride



was selected instead of sodium alkoxides for preparing the sodium salts of the phenols.

Pure 2-benzylphenol and 4-benzylphenol were readily separated from a commercial mixture (Santophen 7) by utilizing the marked difference in the water solubility of their barium salts. The method of Claisen (87) for the *C*-alkylation of phenols was used for the preparation of the intermediate substituted 2-benzylphenols, with extension to heterocyclic systems (table 19, Nos. 42-55). Conversion of the various substituted phenols to the 2-dimethylaminoethyl ethers proceeded smoothly *via* the Williamson ether synthesis.

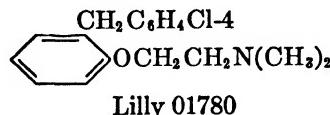
A series of 2-(2-benzylphenoxy)ethyl-2'-chloroethylamines (Nos. 56-79) were prepared for testing as spasmolytics (456).



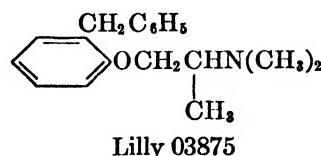
Many of the members possess antihistaminic properties in various degrees, but their primary action is to reverse the pressor effect of epinephrine (*cf.* page 311).

Attachment of the ethanolamine residue directly to a diphenylethane system resulted in quite inactive agents (table 4, Nos. 10 and 11).

The 2-(4-chlorobenzyl)phenyl 2-dimethylaminoethyl ether (Lilly 01780) is an extremely active antagonist (137, 155).

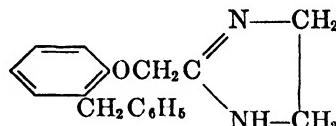


Branching of the side chain at the α -carbon atom more than doubled the activity (460 per cent Benadryl) and prolonged the action (Lilly 03875). Side-chain substitution at the β -carbon atom destroyed antihistaminic activity (344).

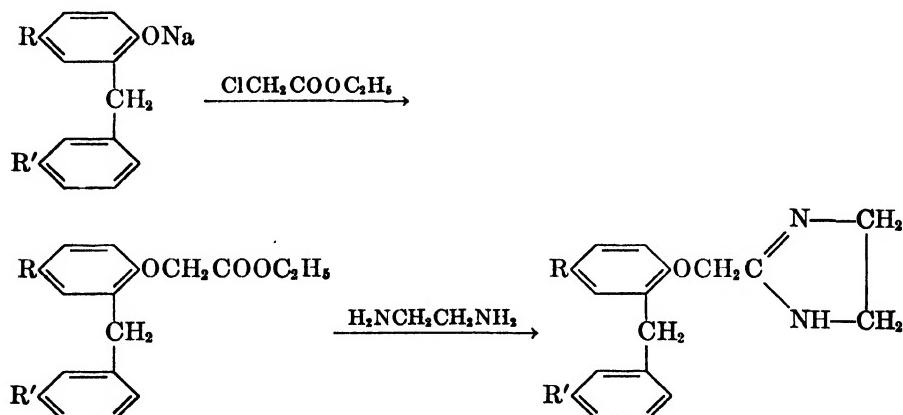


All of the benzylphenols have a sedative effect, which is due to the dialkylaminoethoxy side chain.

The imidazoline analogs of 2-benzylphenyl 2-dimethylaminoethyl ether were recently announced (455). None of the compounds prepared was more active



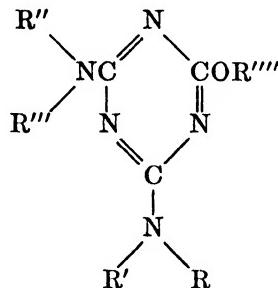
than the dimethyl derivative. They were prepared by converting the appropriate 2-benzylphenols to the sodium derivatives by means of sodium hydride, condensing with chloroethyl acetate, and treating the product with ethylenediamine.



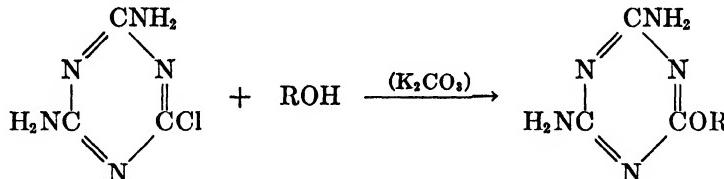
The effect of quaternization on the benzylphenols revealed powerful anti-histaminic activity, but less than that of the tertiary bases (455).

8. Alkoxy-s-triazines

In the search for improved ether antagonists, a large series of triazinyl ethers were synthesized and tested (table 19) (94, 261, 312, 313). The pharmacological properties exhibited by the triazine arsenicals (18) were the impetus for the preparation of the series of alkyl 2,4-diamino-6-s-triazinyl ethers.



The reaction of 2-chloro-4,6-diamino-s-triazine with various alcohols in the presence of potassium carbonate was unsatisfactory. The conditions of the classical Williamson reaction were found suitable.



Of the various types of alcohols employed it was found that the isoalkyl and *sec*-alkyl alcohols took part in the reaction as readily as the primary alcohols. No ether type of product was obtained from the action of the halotriazine on sodium *tert*-butoxide. This was also the case with the sodium derivatives of benzhydrol, fluorenol, xanthhydrol, and menthol. Whether or not this phenomenon was due to steric hindrance was not determined. Since the tautomeric possibilities of the triazine nucleus are limited by the number and arrangement of alkyl substituents on nitrogen, a series of ethers was prepared in which one to four of the hydrogens on the two amino groups were replaced by alkyl groups (table 20, Nos. 24-81).

Examination of the data shows all the triazinyl ethers to be much weaker histamine antagonists than the benzhydryl ethers. The potency of the compounds at first increases with molecular weight and then decreases. The peak lies in the vicinity of the propyl and butyl derivatives (Nos. 3-7) and then decreases (261). Higher homologs, pentoxy to decoxy (Nos. 8-13), were less active. Incorporation of a tertiary amine in the aliphatic chain resulted in inactive compounds, i.e., 2-dimethylaminoethoxy and 2-morpholinoethoxy (Nos. 19 and 21). Of the

two aryloxy derivatives (Nos. 16 and 18), only the phenoxy exhibited some activity. Perhaps the activity of the cyclohexyl ether may be explained on the basis of a similarity in length of the molecule to that of the propyl and butyl ethers. The antihistamine effect of 2-isopropylthio-4,6-diamino-s-triazine (No. 22) is about the same as that of the oxygen analog. Substitution of the amino groups in the 4- and 6-positions of the ring (Nos. 23-25) did not appreciably alter the activity of the unsubstituted compounds.

It is of interest to note that melamine itself, and its derivatives devoid of an ether linkage, were found to be ineffective antihistamine agents. Thus, it is apparent that an ether linkage was necessary within this series. The acute toxicity of the propoxy and butoxy compounds (Nos. 3, 4, 6, and 7) was nearly one-half that of aminophylline, which was used as a reference. Lower homologs possessed low toxicity and activity, whereas higher homologs are more toxic and exhibit low activity, if any.

No orderly variation in activity was noted in the methyl and butyl ethers or with multiple substitution on the amine groups (Nos. 26-83) (312). Nos. 84-99 were prepared to fill in the gaps to determine if any products of appreciable activity had been overlooked. No potent compounds were noted therein (313).

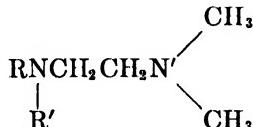
9. 2-(2-Biphenylyloxy)ethyl-2-haloalkylamines

Divergent in structure from the previously described antihistaminics are the substituted 2-haloalkylamines. Although their primary action is to block and reverse the pressor action of epinephrine (*cf.* page 311), their powerful sympatholytic and antihistaminic effect warrants the listing of the series of 2-(2-biphenylyloxy)ethyl-2-haloalkylamines (table 21) (364).

Antihistamine action was greatest with the methyl homolog (No. 2), which was effective in a dose of 1.5 mg./kg. Activity decreased progressively as methyl groups were added to the alkyl chain (Nos. 1, 3, 5, 7-12) and was decreased by substitution of the 2-chloroethyl group (compare Nos. 20 and 3). None of these compounds exerted an antihistamine action comparable in degree to that of Benadryl.

B. DERIVATIVES OF ETHYLENEDIAMINE

Isocyclic and heterocyclic derivatives of ethylenediamine comprise the bulk of and represent the most potent compounds of the antihistaminic drugs. The basis for the present differentiation into isocyclic and heterocyclic derivatives in the typical formula



rests in the *N*-substituents. The structure of the *N'*-substituents does not affect the present classification.

The isocyclic derivatives are subdivided into the *N*-phenylethylenediamines (Fournéau amines), the Rhône-Poulenc isocyclic amines, other isocyclic ethylenediamines, benzhydrylamines, isocyclic-substituted heterocyclics, amides of ethylenediamine, and isocyclic aminomethylimidazolines. The heterocyclic compounds are grouped into monocyclic amines, polyheterocyclic ring structures, and heterocyclic methylimidazoles and methylimidazolines.

1. N-Isocyclic derivatives of ethylenediamine

a. Fournéau amines

After investigating the phenoxyethylamines (table 3), Bovet and Staub (38) turned their improved techniques of antihistamine assays to the study of the *N*-phenylethylenediamines.

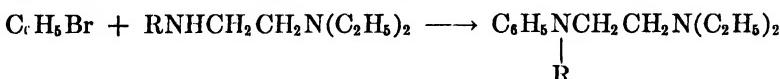
Synthetic research in Fournéau's laboratory (142, 143, 144) had disclosed that sympathomimetic, sympatholytic, and antihistaminic actions are found side by side in these aniline compounds. Staub (407) studied the different ethylenediamines and reached almost the same conclusions as with the phenoxyethylamines (table 22) (*cf.* page 16). Secondary amines were very inferior to the tertiary bases. *N*-(2-Aminoethyl)aniline or *N*-phenylethylenediamine (F 1540) is inactive against histamine, although it is a hypertensor and a bronchodilator. The effects of modifications of F 1571 (V), the most active Fournéau amine, were noted. When the ethyl group was replaced by hydrogen (F 1167), the product was totally inactive. If methyl replaced ethyl (F 1335), the result was rather weak activity. When isopropyl replaced ethyl (F 1709), the compound was distinctly less active. Studies were made of nuclear changes in F 1167 and F 1571. In F 1167, the results were almost exactly as in the phenoxyethylamines. The introduction of a methyl group (F 1332) into the ring did not augment the activity. Further introduction of an isopropyl function (F 1691) to give the *N*-analog of F 1379 (table 3) gave increased potency. The isomer of F 1691 corresponding to F 929 was not investigated, owing to the difficulties of its preparation, but it was supposed that it would correspond, as did F 1167 and F 1379. The parallels noted between the ethers and amines led to the hope that derivatives of F 1699 would be very active, but no activity was found. The modifications of the nucleus of F 1571 did not increase activity, but ring substitution instead decreased the potency in the following order: methylphenyl, dimethylphenyl, isopropylphenyl (F 1599, F 1670, F 1699). At the same time, the anti-spasmodic activity (as measured by the relaxation of acetylcholine-induced spasm) was increased. Exactly the opposite effect was found by Staub (407) to hold true for the phenoxyethylamines. In the latter series, the introduction of methyl, dimethyl, or isopropyl in the phenyl ring increased the antihistamine activity (F 928, F 1655, F 929), while spasmolytic activity was decreased in the same order.

The minimum active dose of F 1571 is 10–15 γ/ml. Five milligrams protected guinea pigs against four to six lethal doses of histamine (38, 51, 109, 170, 175, 311, 329, 407).

N-Phenyl-*N'*,*N'*,*N'*-triethylethylenediamine (F 1571) was first prepared by v. Braun (42) and reported by Schulemann (383).

A series of di- and tri-substituted aryl diamines, among which was F 1571, were prepared for study by J. P. Fourneau and Lestrange (144) (table 23). The disubstituted bases were prepared *via* the *N*-substituted phthalimides, which were cleaved by hydrochloric acid, except for the methoxyaryls which required hydrazine for cleavage. The trisubstituted diamines were synthesized by heating the arylamine in a sealed tube with the appropriate dialkylaminoalkyl halide.

Alternate methods of synthesis involve the condensation of a dialkylaminoalkyl-substituted amine with an alkyl, aryl, or aralkyl halide or the reaction of the aryl halide with an asymmetrically trisubstituted alkylenediamine. The



reactions are best carried out at higher temperatures in solvents like benzene and toluene and in the presence of a neutralizing agent such as potassium carbonate or sodium amide.

b. Rhône-Poulenc isocyclic amines

Research in the laboratories of the Société des usines chimiques Rhône-Poulenc (Paris) soon revealed that the changing of the diethyl group in F 1571 to dimethyl (RP 2325, VI) improved the antihistaminic activity (histamine aerosol test) fourfold and decreased the toxicity considerably. Furthermore, it was found that further improvement could be obtained by replacing the ethyl of the dimethyl homolog by benzyl (RP 2339, Antergan, VII). This change produced an increase in the antiasthma activity of twenty times over that of F 1571 (175). From there research led to the synthesis of a number of compounds (tables 24 and 24A), the majority of which are homologs of RP 2325 (VI) and RP 2339 (VII).

Viaud (443), in a review of the RP compounds, drew the following conclusions regarding structure and activity: variations at the end of the aliphatic side chain of RP 2325 and RP 2339 (substituting for dimethylamino, amino, diethylamino, etc.) resulted in almost complete loss of activity (RP 2315, 2358, 2650, 2323, 2762, 2835); replacement of the benzyl group in RP 2339 by hydrogen, methyl, ethyl, allylphenyl, *p*-ethylbenzyl, and phenethyl resulted in decisive loss of activity (RP 2236, 2337, 2325, 2342, 2347, 2338, 2757, 2612, 2614, 2349, 2744, 2355, 2637, 2354, 2768, 2565, 2352, 2621).

Substitution of the benzyl group in RP 2339 by certain oxygen-interrupted aliphatic chains, such as —CH₂CH₂OCH₃ (RP 2887) or —CH₂CH₂OC₂H₅ (RP 2796) gave compounds of still considerable activity, while substitution by —CH₂COOC₂H₅ (RP 2846) or —CH₂CH₂N(CH₃)₂ (RP 2368) gave inactive compounds. A compound with a sulfur-interrupted side chain, —CH₂COCH₂SCH=NH (RP 2776), had considerable activity.

The length of the aliphatic side chain was found not to be the sole determinant of activity, but potency is dependent on other parts of the molecule.

Substitution in the phenyl ring of RP 2339 by *p*-methyl (RP 2639) maintained the original activity, while amino substitution in the para position (RP 2378) or substitution of the phenyl by cyclohexyl (RP 2497) or benzyl (RP 2503) resulted in complete loss of activity.

Several other far-reaching changes, such as substitution of the phenyl group in RP 2325 by the *p*-*N*-ethyl-*N*-(2-dimethylaminoethyl)amino group (RP 2902) and others (RP 2889, RP 3110) gave only inactive compounds.

RP 2339 (VII) was prepared by condensing *N*-benzylaniline with 2-(dimethylamino)ethyl chloride in the presence of potassium carbonate (64). The others were synthesized by the proper modification of the previously mentioned methods.

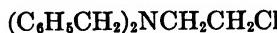
c. Other isocyclic ethylenediamines

Early European and American investigators, unaware of the various Rhône-Poulenc isocyclic compounds, synthesized many of the RP compounds (table 24), among other structures.

Table 25 lists the constants of the other isocyclic ethylenediamines. The pharmacological data are slight. *N*-Phenyl-*N*-benzyl-*N'*-(1-piperidyl)ethylenediamine (No. 23) possessed 0.2 of the activity of Antergan, while the *N*-methyl analog (No. 51) had only 0.05 of the activity of Antergan. With the exception of the *N*-(2-haloalkyl)-1-naphthalenemethylamine derivatives (Nos. 34-47), none of the compounds are more active than Antergan. The 3,4-dioxymethylene aryls (Nos. 53 and 54) are much less effective than Benadryl (307).

The series of *N*-(2-haloalkyl)naphthalenemethylamine derivatives (Nos. 34-50) tested by Loew and Micetich (265) and synthesized by Rieveschl and co-workers (361) belong in the class of adrenergic blocking drugs (*cf.* pages 311-312). They are also quite potent antihistamine drugs. Activity was greatest with the lower alkyl homologs (Nos. 34-36) which contained a 2-chloroethyl or 2-bromoethyl group, the ethyl homologs being the most active. Diminution of histamine-induced bronchospasm was progressively lessened as additional carbon atoms were added to the alkyl groups (Nos. 37-44). Activity was lost if the 2-chloroethyl was replaced by 2-hydroxyethyl (No. 47). The bis-(2-chloroethyl) compound (No. 46) was quite weak. Substitution of chlorine in the 4-position of the naphthalene ring (No. 50) decreased activity. The two *N*-ethyl compounds (Nos. 35 and 36) proved to be about as effective as Pyranisamine, an extremely potent agent (table 1, No. 15).

The antihistaminic activity of seventy-five congeners of Dibenamine [*N*-(2-chloroethyl)dibenzylamine] revealed (304) that the antihistaminic properties



Dibenamine

were independent of significant cholinergic blocking activity. Antihistaminic activity was not parallel to adrenergic blocking activity. The 2-haloalkyl group is essential for high activity. Substitution of a 2-dimethylaminoethyl radical, which provides maximal activity in most series of antihistaminics, leads to inactivation. Phenoxyethyl- (particularly 2-substituted) and 1-naphthalene-

methylamines are the most active. Unsymmetrical *N*-phenoxyethyl-*N*-benzylamines are almost always more active than the *N*-diphenoxymethylamine or *N*-phenoxyethyl-*N*-ethylamine analogs.

The use of sodium iodide, copper powder, and cupric chloride catalysts proved advantageous for the preparation of some of the tertiary amines (396).

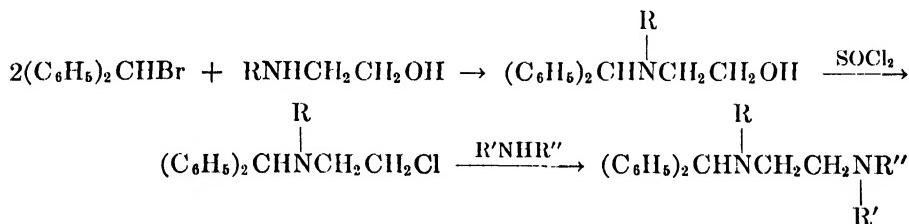
d. Benzhydrylamines

The replacement of the ether linkage by —NH in benzhydryl compounds (*cf.* pages 317-321) (tables 5 and 6) has usually led to weaker and inactive compounds.



Table 26 lists the amine analogs of the ethers, studied by Loew, Kaiser, and Moore (263) (table 5, Nos. 3, 6, 7, and 9), which proved practically inactive. In a series of ring-substituted benzhydrylamines tested the *p*-phenoxy compounds (table 27, Nos. 16 and 17) were the most active. No physical constants were given (4).

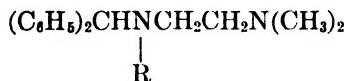
N-Substituted benzhydrylamines were synthesized by the reaction of benzhydryl bromide with ethanolamines in benzene solution, and then conversion of the *N*-benzhydrylethanolamines to the 2-chloroethylamines by reaction with thionyl chloride in chloroform solution. The 2-chloroethylamines were condensed with secondary amines to give the substituted ethylenediamines (98) (table 28).



It is necessary to run the initial condensation in a nonpolar medium, for in a reactive solvent such as ethanol it is possible for the benzhydryl ether to form instead of the desired benzhydrylamine (98).

Pharmacological data for the various *N*-substituted benzhydrylamines (table 28) were not reported.

Alles and Redemann (6) (*cf.* page 319) studied three benzhydrylamines: (β -diphenylmethylaminoethyl)dimethylamine and the *N*-methyl and *N*-ethyl analogs ($R = H, C_2H_5, C_2H_6$). Their results showed that the compounds of the di-



amine system were not quite as active as the ethers (table 6A). The activity of the methosulfate of the ethyl compound was close to that of the tertiary methyl derivative.

An alternate method of synthesis involves the condensation of benzhydrylamine and an appropriately substituted halide. Benzhydrylamine has recently been prepared from benzophenone oxime, both by reduction with sodium in ethanol and by hydrogenation over Raney nickel (185).

The lower alkyl members of the series of benzhydryl-2-haloalkylamines



(table 28, No. 4, and table 29) have both very slight antihistaminic activity and moderate epinephrine-blocking activity (259). Those with higher alkyl groups had only the latter activity. Table 29 lists a series of haloamines synthesized by Rieveschl and Fleming (363) and investigated by Loew and coworkers (259). The haloamines were prepared by heating substituted benzhydrylethanolamines with thionyl chloride or phosphorus oxychloride (362).

* The 2-haloalkynaphthalene derivatives (table 25, Nos. 34-47) were much more potent antihistaminics than the benzhydryl analogs, while the *N*-alkyl-2-(2-biphenyloxy)-2'-diethylamines (table 21) exerted a moderate degree of antihistamine action and stronger adrenergic blocking action than the benzhydryl derivatives (265).

Nickerson and Gump (303) have brilliantly covered the chemical basis for adrenergic blocking activity in compounds related to Dibenamine.

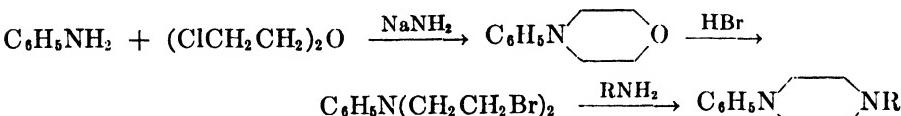
The benzhydrylpiperazine derivatives are the most potent of the benzhydrylamine derivatives, and will be discussed in the succeeding section.

e. *N*-Isocyclic substituted heterocycles

Among the different heterocyclic nitrogen groups, piperazine and piperidine are the only ones in which a significant amount of work has been done with isocyclic substituents, with a view toward antihistaminic action.

Cerkovnikov and coworkers (73, 74, 75) prepared a number of mono- and 1,4-disubstituted derivatives (table 30) whose activities varied from nil to moderate. The most active initial compound was 1-phenyl-4-(2-dimethylaminoethyl)piperazine (No. 6). Fifty milligrams protected guinea pigs against eight lethal doses of histamine. This effect is very weak as compared to that of the more potent antihistamines (table 1). The benzyl analog (No. 19) was a weaker antagonist.

The 1-phenylpiperazine derivatives were synthesized from 4-phenylmorpholine, prepared from aniline and bis(2-chloroethyl) ether. The morpholine compound yielded *N,N*-bis(2-bromoethyl)aniline on hydrolysis in a sealed tube with hydrobromic acid. Treatment with substituted amines yielded the phenylpiperazine derivatives.



The 1-benzylpiperazine (No. 19) was prepared in a like manner from 4-benzylmorpholine.

1-Phenyl-4-(2-dimethylaminoethyl)piperazine (No. 6) having been found to possess considerable activity, a number of other *N*-heterocyclic compounds containing an ω -dimethylaminoalkyl group attached to the nitrogen atom were synthesized and their pharmacological properties compared (table 30, Nos. 22-28) (75).

All the substances were prepared by boiling the desired amine with the corresponding heterocyclic compound in the form of a halo derivative. The tertiary bases were isolated as the *p*-toluenesulfonyl chlorides.

Comparison of the data in table 30 shows certain definite regularities. Activity is present where the aliphatic substituent contains an ethyl or propyl chain. However, an increase in length by one methylene group lowered the potency (*cf.* Nos. 6 and 22). When the ethyl chain carries a dimethylamino group in the 2-position, the antihistaminic activity is present to a higher degree than when the $-\text{CH}_2\text{CH}_2-$ group is joined to an oxygen atom (ether), as seen from a comparison of Nos. 6 and 29. On the other hand, the effect of a heterocyclic nucleus is also very great. When the 2-dimethylaminoethyl group is attached to a morpholine nucleus (No. 28), the activity is abolished. When it is attached to a piperidine nucleus, slight activity results (No. 27). Introduction of a piperazine nucleus raises the potency considerably (sixteen times), as can be noted by comparing Nos. 27 and 6. The dimethylamino group is important with regard to both its presence and its relative position. Thus, when this group is attached directly to the heterocyclic nucleus, activity is present, while if a methylene group is interposed, the potency is zero (*cf.* Nos. 24 and 26). Introduction of two dimethylamino groups increases the antihistaminic activity nearly twice, as seen from comparing No. 22 and No. 23. The nature of the second substituent on the heterocyclic nucleus is also of significance. Nos. 24 and 25 have the same aliphatic substituent in the same position, but one carries a phenyl group and is active, while the methyl-containing compound has zero potency.

The toxicity is also greatly influenced by constitution. The phenyl group on the heterocyclic nucleus definitely increases toxicity (*cf.* Nos. 24, 25, and 27). The position of the dimethylamino group, as well as the number of groups, also influences the toxicity. When the group is attached directly to the heterocyclic nucleus, the compound (No. 24) is toxic to mice. When a methylene group is interposed, the toxicity increases (No. 26), and when an ethyl group replaces a methyl group the tolerance is much higher (Nos. 6 and 27). When a propyl group is used instead, the lethal dose for mice is slightly higher than when the ethyl group is used (Nos. 6 and 22). Introduction of a second dimethylamino group into the same (ethyl) chain increases the toxicity more than fivefold (Nos. 6 and 23).

4-Dimethylamino-1-phenylpiperidine (Irenal) (No. 24) had previously been shown to be a relatively potent spasmolytic (411). It was prepared from 1,5-dibromo-3-dimethylaminopentane hydrobromide and aniline by heating in a sealed tube (72).

The antihistaminic activity of a series of dibenzylpiperazines (table 31) (243, 284) did not reveal potent antihistamines. Antergan (RP 2339) is three times more active than the most active derivative (No. 1). The activities of Nos. 1 and 4 are comparable and four times that of No. 3.

Two independent investigations of substituted piperazines, simultaneously proceeding in the laboratories of Burroughs Wellcome and Company, Tuckahoe, New York, and the Abbott Company, Chicago, Illinois, reached the identical conclusion that *N*-methyl-*N'*-benzhydrylpiperazine (table 33, No. 1) was an active histamine antagonist, equal to Benadryl in potency.

Benzylmethyl- and benzylethyl-piperazines, when tested by the tracheal chain method (*cf.* page 313) at the laboratories of Burroughs Wellcome and Company, were found to have 1 per cent and 0.4 per cent, respectively, of the antihistaminic activity of Benadryl (15). This suggested that *N*-methylpiperazines having *N'*-substituents containing two or three rings would be active antagonists and prompted the preparation of a variety of derivatives of methylpiperazine (table 32) (5).

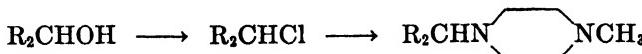
The α -phenylphenacyl derivative (No. 10) was much less potent than 1-benzhydryl-4-methylpiperazine (table 33, No. 1) and the 1-phenyl-2-hydroxyphenethyl and 1-phenyl-1-(4-hydroxyphenacyl) compounds (Nos. 11 and 12) had only vestigial activity. Nos. 1-5 had activities intermediate between those of 1-benzyl-4-methylpiperazine (No. 13) and 1-benzhydryl-4-methylpiperazine. Nos. 6-9 showed little or no activity.

The benzhydryl group appeared, from the above, to be close to the optimal size desired for antihistaminic activity.

With the exception of Nos. 3 and 11, all the substances listed in table 32 were prepared by the direct action of methylpiperazine with the appropriate halide. No. 3 was prepared by catalytic hydrogenation of the nitro compound (No. 2), while No. 11 resulted from reduction of the phenacyl precursor with aluminum isoproxide. Hydrogenation of the phenacyl derivative with Adams' catalyst resulted in debenzylation.

N-Benzhydryl-*N'*-methylpiperazine (table 33, No. 1) was found to possess the same activity as Benadryl (66, 67, 68). Its toxicity was also very similar to that of Benadryl.

Table 33 lists the series of *N*-benzhydryl-*N'*-methylpiperazines prepared by Baltzly and coworkers (16). Synthesis of the benzhydrylmethylpiperazines proceeded from the benzhydrol through the halide and final reaction with methyl-



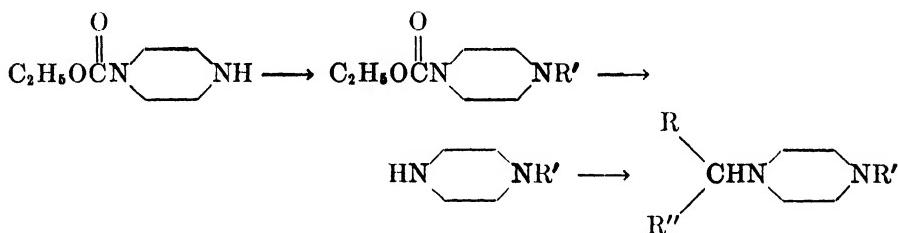
piperazine. Some of the required carbinols were prepared directly from the appropriate aldehydes and Grignard reagents. The others resulted from the reduction of the corresponding ketones.

Quaternization of the methyl-bearing nitrogen atom (No. 2) largely abolished activity. Nos. 3 and 18, in which one cyclohexyl replaces phenyl, also showed diminished potency.

Nos. 6, 15, and 17, wherein the benzhydryl substitution was *p*-chloro, *o*-methoxy, and *p*-methoxy, respectively, were less toxic than the parent substance (No. 1), No. 6 being about one-half and No. 17 about one-third as toxic. Nos. 15 and 18 appeared respectively to be slightly less and slightly more potent than No. 1. No. 6 (Perazil, table 1, No. 17) was very potent and persistent in action. No. 17 was virtually impotent when tested *in vivo*. This is probably due to instability, since it is rapidly cleaved in warm aqueous and alcoholic solutions to methylpiperazine and neutral fragments. The *o*-methoxy compound (No. 15) is considerably more stable. Table 34 lists the antihistamine activities of some of the aforementioned substituted piperazines (68).

Independent investigation in the Abbott Laboratories verified the activity of 1-(*p*-chlorobenzhydryl)-4-methylpiperazine. Table 35 lists the group of 1-substituted and 1,4-disubstituted piperazines prepared there by Hamlin and co-workers (183, 184).

The unsymmetrical 1,4-disubstituted piperazines were prepared through the use of 1-carbethoxypiperazine. The low-molecular-weight group was added and then the ester group removed with concentrated hydrochloric acid. The final alkylation was accomplished with the appropriate halide, with the aid of an

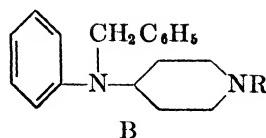
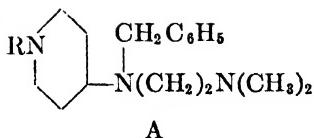


acid-binding agent. With the more stable benzhydryl chlorides and 1-methylpiperazine the yields were good. As R' (table 35) increased in molecular weight, the yields progressively decreased, as was the case for the less stable benzhydryl halides.

With the exception of the 1-(9-fluorenyl)piperazines (Nos. 34-37), all the 1-substituted and 1,4-disubstituted piperazines (Nos. 23-33, 38, 39) were prepared in a manner essentially parallel to that of Baltzly and coworkers (15), where the appropriate halide was reacted with anhydrous piperazine. 1-(9-Fluorenyl)piperazine was made *via* the carbethoxypiperazine method.

A series of 1,4-diheterocyclic substituted piperazines recently proved to be potent analgesics (110), while sym-dialkylpiperazines, containing long-chain alkyl radicals, were made for testing as germicides (391).

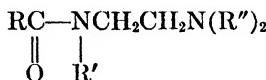
Certain 4-aminopiperidines were prepared as potential antihistaminic agents, on the basis of their structural analogy to *N,N*-dialkyl-*N'*-benzyl-*N'*-aryl(or heterocyclic)ethylenediamines (342). The 4-aminopiperidines could be classified with both the isocyclic and the heterocyclic derivatives, for the piperidine group has been substituted for the phenyl group in A and for the ethylenediamine group in B (table 36).



All the alkyl and isocyclic derivatives showed rather weak activity. The necessary piperidones were made by condensation of methylamine or ethylamine with methyl acrylate and subsequent cyclization. Reductive alkylation of primary amines with the piperidones yielded the substituted 4-aminopiperidines. The secondary amines were alkylated with benzyl bromide to yield No. 5 (in table 36).

f. Amides of ethylenediamine

The effect of substituting RCO for the R radical in the general formula

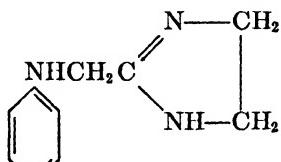


to produce a series of amides of ethylenediamine was studied by Villani and coworkers (table 37) (444). The amides were prepared by the reaction of aryl or heterocyclic acid chlorides with the appropriately substituted ethylenediamines. The condensations were carried out in the presence of a tertiary amine such as pyridine, triethylamine, or dimethylaniline. In the case of the picolinoyl amides, pyridine could not be employed as the solvent because of the ease with which picolinoyl chloride forms colored complexes with pyridine. A mixture of triethylamine and anhydrous benzene was suitable.

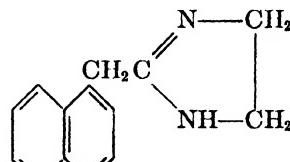
Nos. 24-27 had an activity approximately 0.1 that of Trimeton (table 1, No. 26). Nos. 2, 3, 9, 12, and 23 had 0.2 the activity orally and subcutaneously. No. 22 possessed 0.4-0.5 the potency by either route of administration. The remainder of the substances showed approximately 0.01 the activity orally and 0.01-0.02 subcutaneously. The amides might have been classified with the heterocyclics.

g. N-Isocyclic aminomethylimidazolines

2-(*N*-Benzylanilinomethyl)-2-imidazoline, Antistine (table 1, No. 2), is the most prominent of the chemical family where the dialkylaminoethyl side chain is replaced by the more complex imidazoline (dihydroglyoxaline) function. Antistine is similar to the sympathomimetic drugs Otrivine [(2-anilinomethyl)-2-imidazoline] and Privine [2-(1-naphthylmethyl)-2-imidazoline].



Otrivine

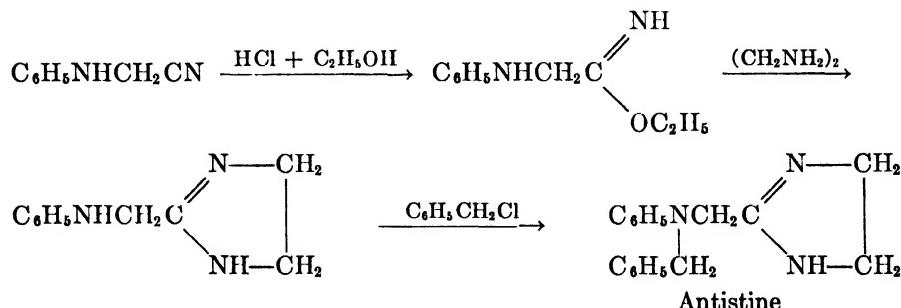


Privine

Antistine appears to exercise an antihistaminic action slightly less than that of Antergan (table 25, No. 1). Although the substitution of an imidazoline group slightly reduces the pharmacological activity, there is such clinical tolerance that it can be used for local administration to sensitive organs such as the eye, ear, and nose.

Antistine is synthesized from anilinomethylimidazoline, which is prepared from anilinoacetimidooester and ethylenediamine (110). The 2-(*N*-benzylanilino-methyl)-2-imidazoline is then formed by the reaction with benzyl chloride

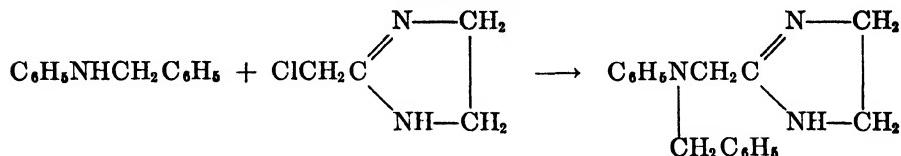
Method A



(method A) (86). The 2-imidazolines can be prepared directly from the nitrile and an aliphatic diamine, if the two amino groups of the latter are attached to vicinal carbon atoms. Hydrogen sulfide, carbon disulfide, phosphorus pentasulfide, aluminum trisulfide, ferrous sulfide, and sodium sulfide are catalysts for the reaction (206). A recent patent claims the production of imidazolines when *N*-aryl-*N*-aralkylaminoalkylcarboxylic acids or their derivatives are treated with an aliphatic 1,2-diamine (207).

An alternative synthetic method for the *N*-substituted imidazolines involves the condensation of 2-(chloromethyl)-2-imidazoline and the appropriate isocyclic

Method B



secondary amine (méthod B) (285). 2-(Chloromethyl)-2-imidazoline is prepared from the 2-chloroethylimidooester and ethylenediamine at 0°C. (397a).

Table 38 lists the series of *N*-isocyclic substituted imidazolines prepared for testing. The ether analogs (table 11) appear to be more potent, but this is overshadowed by their toxicity. Practically all the compounds were synthesized by Miescher and coworkers in Switzerland. The pharmacological data on all except Antistine (No. 8) are nil, but no improvements in activity seem to have been achieved by ring substitutions or variations in the side chain. 2-*N*-*p*'-Tolyl-

N-(*m*-hydroxyphenyl)aminomethyl-2-imidazoline (No. 6) possesses weak antihistaminic activity but is a potent adrenergic drug (188) (*cf.* pages 311-312).

The series of diphenylaminomethylimidazolines (Nos. 3-7) was prepared by heating substituted diphenylamines with 2-(chloromethyl)-2-imidazoline in an atmosphere of nitrogen (287).

The tetrahydropyrimidine analog of Antistine (No. 26) has insignificant activity (230). The compound was prepared from the condensation of ethyl *N*-phenylaminoacetate and benzyl chloride to yield ethyl *N*-benzyl-*N*-phenylaminoacetate, which was then refluxed with trimethylenediamine.

In the course of an extensive investigation of amidines, Oxley and Short (310) found that 2-substituted imidazolines and their ring homologs were obtained in good yield by heating *N*-substituted amidinium salts with an alkylidendiamine. An extensive series of imidazoline intermediates, valuable in the synthesis of the types found in table 37, were prepared. 2-Arylmethyl-1-alkylimidazolines were likewise prepared by the interaction of the appropriate cyanide with a salt of *N*-methyl- or *N*-ethyl-ethylenediamine.

h. Anilino-*s*-triazines

The weak antihistaminic properties exhibited by the alkoxy-*s*-triazines (*cf.* page 329, table 19) suggested the investigation of anilino-*s*-triazines (446). Table 39 lists the prepared triazines, in which extremely small potency appeared.

2. *N*-Heterocyclic derivatives of ethylenediamine

The majority of potent histamine antagonists are found in this group, wherein the aryl functions are replaced by various mono- and poly-cyclic heterocyclic groups. An analogous situation resulted when heterocyclic nitrogen moieties were introduced into the sulfanilamide derivatives (306).

Since the initial and most productive work was performed at the Rhône-Poulenc laboratories, a special section is devoted to this research. Various heterocyclic functions are included in the "RP" investigations and will be grouped together in tables 40 and 50. The remainder of the monocyclic hetero functions will be classified according to individual structures.

a. *N*-Monoheterocyclic derivatives of ethylenediamine

(1) Rhône-Poulenc monoheterocyclic diamines

In 1944 Bovet and coworkers (34, 35, 40) described the properties of derivatives of 2-aminopyridine culminating in Neoantergan (table 1, No. 15), which still remains among the most potent of the antihistaminic drugs.

Table 40 lists the various *N*-heterocyclic derivatives of ethylenediamine, prepared at the laboratories of the Société des usines chimiques Rhône-Poulenc (*cf.* isocyclic amines, pages 332-333, table 24).

Viaud (443) drew the following relationships between structure and activity (*cf.* 200): replacement of the benzyl group in Antergan (RP 2339) by various heterocyclic groups resulted in either loss of activity, or similar potency. The 2-phenyl derivative (RP 2740) was inactive. The 2-furfuryl analog (RP 2747)

possessed little activity. The 2-tetrahydrofurfuryl (RP 2749) and the 2-methylthiazole (RP 2764) compounds had the same activity as Antergan. The pyridine analog (RP 2972) and others (RP 2758, 2764, 2765, 2788, 2880, 2895) were compounds of little pharmacological interest.

The replacement of the phenyl group in Antergan by heterocycles resulted in major improvements. The 2-pyridyl compound (RP 2750) was twice as active as Antergan. Further substitution in the benzyl group by *p*-methoxy gave Neoantergan (RP 2786) with fivefold the activity of the 2-pyridyl derivative (RP 2750) and ten times that of Antergan. If the methoxy group was in the ortho position (RP 2855) or meta position (RP 3325), the activity disappeared completely. Substitution by *p*-methyl (RP 2932) lowered the activity to that of Antergan, while *p*-ethyl (RP 2910) caused almost complete disappearance of activity. Branching of the aliphatic side chain in Neoantergan (RP 3420, RP 3427) or increase of the length of the chain (RP 2800) lowered the activity considerably. Substitution in the pyridine ring of Neoantergan by one (RP 2890) or two methyl groups (RP 2933) suppressed the activity. The 3- (RP 2938) and 4-pyridyl (RP 2958) compounds were almost completely inactive. The 2-pyrimidyl (RP 2971) and 2-thiazolyl (RP 2909) derivatives were inactive. The replacement of the *p*-methoxybenzyl group in Neoantergan by furfuryl (RP 2803) lowered the activity to that of RP 2750. Many of the observations have been disputed by American investigators. Compounds which have been declared almost impotent by the Rhône-Poulenc pharmacologists have appeared among the prominent commercial drugs (RP 2740, 2971, 2764; table 1, Nos. 9, 12, 27).

Neoantergan was prepared by the reaction of 2-(2-dimethylaminoethylamino)-pyridine with *p*-methoxybenzyl chloride in the presence of sodium amide or by the reaction of 2-(*N*-*p*-methoxybenzyl)aminopyridine with 2-dimethylaminoethyl chloride (443).

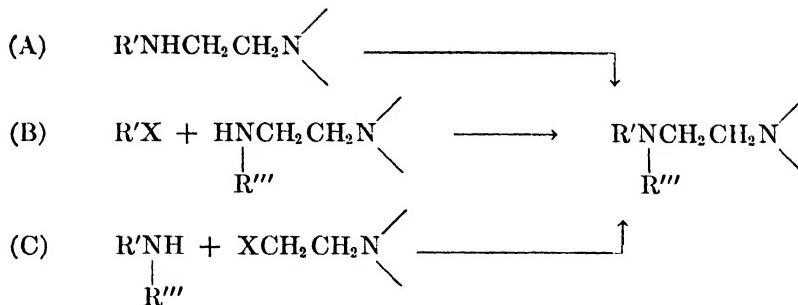
(2) Monoheterocyclic compounds other than Rhône-Poulenc compounds

(a) Pyridine derivatives

The extensive work of the Rhône-Poulenc investigators (pages 341-342) not being known, research on the replacement of the aryl groups of the Fourneau diamines (pages 331-332) by heterocyclic radicals progressed independently at the laboratory of the Ciba Pharmaceutical Company in New Jersey (112, 203, 278) and culminated in the preparation and testing of Pyribenzamine (table 1, No. 19).

Various basically substituted tertiary pyridine compounds (table 41, Nos. 1, 2, 4, 14, 35-37, 39, 40, 45-49, 59, 60, 62, 69, 100-109) were prepared by condensing the dialkylaminoethyl substituted-amino heterocyclic compound with an alkyl or aralkyl halide (A), by condensing the halogenated heterocyclic substance with an asymmetrically trisubstituted alkylendiamine (B), or by condensing the alkyl- or aralkyl-amino heterocyclic derivative with a dialkylaminoethyl halide (C).

The necessary secondary amines were prepared by condensing primary amines with a dialkylaminoethyl halide in toluene solution in the presence of sodium or



lithium amide (203, 457). This method was preferred to that of condensing the asymmetrically substituted diamine with a halogen-substituted heterocyclic compound. All the secondary amines were found to be inactive, in contrast to the tertiary bases, which exhibited considerable range of activity (table 41).

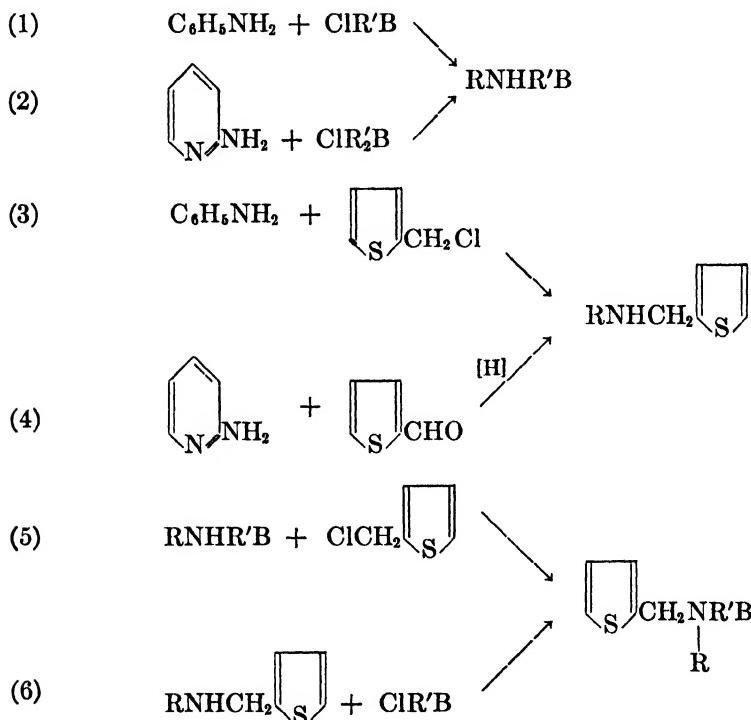
The research of Huttner and coworkers confirmed many of the findings of Viaud (443) with the RP compounds. The 2-pyridyl-substituted compounds were the most active (table 41, Nos. 1, 4, 14, 35-37, 39, 40, 45-49, 59, 60, 62, 69), with the benzyl derivatives being the most potent (Nos. 1, 4, 59, 60, 101, 103, 104, 106, 108). The dimethylaminoethyl side chain was by far the most reactive, for replacement by diethyl (Nos. 37, 40, 43, 48, 108), piperidyl (Nos. 59, 60), or morpholinyl (No. 62) caused severe decreases in activity. Alkyl substituents (Nos. 35-38, 59), acyl (No. 46), aryl (Nos. 39, 40, 69, 100, 109), or the dipyriddy-substituted derivatives (Nos. 47, 48, 49, 105, 107) were all ineffective as compared with Pyribenzamine (No. 1) or Neoantergan (No. 4). The phenethyl compound (No. 2) was practically inactive. The introduction of chlorine in the pyridine ring almost doubled the activity of the Pyribenzamine type (No. 71), while the toxicity was only slightly elevated. A simultaneous introduction of chlorine and methoxy in the pyridine and phenyl ring, respectively (No. 73), resulted in decreased activity, but also in an appreciable lowering of acute toxicity. A *p*-isopropoxy substituent in the benzyl moiety of Pyribenzamine (No. 6) markedly enhanced the antihistaminic activity and lowered the acute toxicity of the parent compound (25). This follows the effect of the *p*-methoxy group in Neoantergan. However, an ethoxy group in the same position (RP 2843) did not seem to bring about any change in activity (443).

The replacement of the benzyl group by 2,2-dibutylhexyl (table 41, Nos. 66 and 67) was investigated (403) to determine whether this highly branched group would show greater activity than the lower alkyl groups (table 41, Nos. 35, 36, 59). The dimethyl derivative (No. 66) had approximately 1/250 the antihistaminic activity of Pyribenzamine, while the diethyl homolog (No. 67) was 1/5-1/10 as active as No. 66. The synthesis was carried out by the condensation of 2-bromopyridine and (2,2-dibutylhexyl)amine in xylene or cymene solution in the presence of anhydrous sodium carbonate. The *N*-(2,2-dibutylhexyl)-2-aminopyridine was alkylated with the dialkylaminoethyl chloride. Attempts to condense *N,N*-diethyl-*N'*-(2,2-dibutylhexyl)ethylenediamine and 2-bromopyridine with sodium amide were unsuccessful.

Quaternization of Pyribenzamine, Neoantergan, or Antergan did not affect their activity, but their toxicity seems to have been slightly decreased (211).

The principle of isosterism was applied in the preparation of the thiophene analogs (table 41, Nos. 21-32, 51-53, 57, 58, 61, 65, 68, 74-77; table 42). These compounds proved practically as potent as their benzyl or pyridyl analogs.

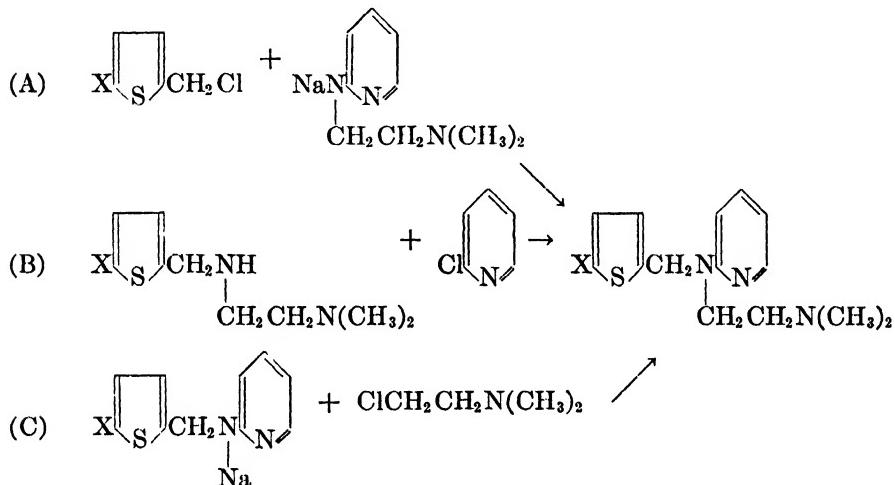
The preparation of the 2-thienyl analog of Pyribenzamine (table 41, No. 21; Table 1, No. 24; Thenylene, Histadyl) was prepared practically simultaneously by a number of laboratories (90, 228, 242, 452). The tertiary amine was obtained by the alkylation of the appropriate secondary amine in benzene or toluene solution in the presence of sodium amide (90, 242, 452) (procedures 5 and 6). The intermediate secondary amines were prepared by condensing aniline with a dialkylaminoalkyl chloride or 2-thienyl chloride (procedures 1 and 3) and 2-aminopyridine with a dialkylaminoalkyl chloride or 2-thiophenealdehyde, followed by reduction (procedures 2 and 4).



The effects of substitution in the thiophene and pyridine rings were studied by a research group at the American Cyanamid Company (88, 90, 442). The 5-halogenated thiophenes (Chlorothen and Bromothen; Table 41, Nos. 24 and 25; Table 1, Nos. 22 and 5) were more active than Pyribenzamine, being twice as active and possessing one-half the acute toxicity on a weight basis. When equal doses of the drugs were administered, Chlorothen and Bromothen protected against histamine shock twice as long as Pyribenzamine (256). In a series

of *N,N*-dimethyl-*N'*-2-pyridyl-*N*-thenylethylenediamines, prepared by Clark and coworkers (90) (table 41, Nos. 23, 24, 27, 28, 32, 51, 52, 74-77), none was as active as Bromothen or Chlorothen.

The compounds were synthesized by the reaction of the 5-halo-2-thenyl halides with the sodium salt of *N,N*-dimethyl-*N'*-2-pyridylethylenediamine (A), by the condensation of 2-chloropyridine with *N,N*-dimethyl-(*N'*-5-chloro-2-thenyl)-ethylenediamine (B), and by the reaction of *N,N*-dimethylaminoethyl chloride and 2-(5-bromo-2-thenyl)aminopyridine (C).



The thenyl halides were usually prepared by chloromethylation in the 1-position. If both 1-positions were substituted, chloromethylation occurred in the 2-position. Alternate methods involved the bromination of various 2-methylthiophenes with *N*-bromosuccinimide and treatment of alkyl 2-thienyl carbinols with hydrogen bromide in benzene.

In view of the increased activity brought about by introduction of the halogen into the thiophene group, it was decided to investigate the effect of halogenation on the antihistamine activity of *N,N*-dimethyl-*N'*-benzyl-*N'*-(2-pyridyl)ethylenediamine (442). The compounds (table 41, Nos. 7-12) where pyridine is unsubstituted were prepared by the condensation of *N,N*-dimethyl-*N'*-(2-pyridyl)ethylenediamine with the appropriate halogenated benzyl halide in the presence of alkali amide or hydride. The highest activity is found in those derivatives halogenated in the 4-position of the benzyl group, and this activity increases as the electronegativity of the substituent increases and its atomic weight decreases from iodo to fluoro. The 4-bromobenzyl derivative has approximately the same activity as Pyribenzamine but the 4-fluorobenzyl derivative is three to four times as active. Halogen substituents in the 2- or 3-position of the benzyl group or in the 5-position of the pyridyl group (table 41, Nos. 70, 71) led to essentially inactive compounds. In the dihalogenated compound (No. 72), the same disadvantageous result occurred.

The replacement of the dimethylaminoethyl group by a dialkylaminoacetyl group (table 41, Nos. 78 and 79) resulted in inactive compounds, as did the 1-naphthalenemethyl derivative (table 41, No. 34) and the *n*-hexyl compound (table 41, No. 17).

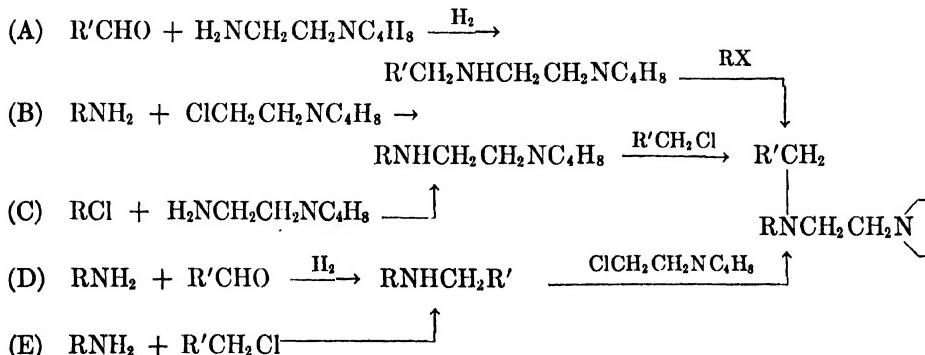
Campagne and coworkers (59, 60, 61) studied the synthesis and reactions of 3-substituted thiophenes and prepared four *N*-substituted dimethylaminoethyl-pyridines containing the 3-thenyl and halogen-substituted 3-thenyl nucleus (table 41, Nos. 28-31). The compounds were synthesized by the reaction of the sodium derivative of 2-(dimethylaminoethylamino)pyridine with the appropriate 3-thenyl bromide, obtained when the proper 3-methylthiophene reacted with *N*-bromosuccinimide (60).

The 3-phenyl compounds all possessed activities about equal to those of Thenylene (the 2-phenyl analog) and Pyribenzamine. The unsubstituted derivative (Thenfadil, table 1, No. 23; table 41, No. 29) is more potent than the chloro- and bromo-substituted analogs. The three compounds (No. 29-31) appear to be of the same order of toxicity as Pyribenzamine when administered intravenously in mice, while Benadryl is approximately one-half as toxic. The two halogenated derivatives appear to be less toxic than the parent compound, the chloro (No. 31) being less toxic than the bromo (No. 30) by subcutaneous injection (192, 235).

The difference between the increased activity on halogenation in the 2-thenyl series and the lack of this in the 3-thenyl analogs is attributed to the difference in the position of the halogen atoms, being 5- in the former and 2- in the 3-thenyl series (235).

The derivatives of 4-aminopiperidine (*cf.* table 36 and page 338) demonstrated that these compounds (table 41, Nos. 85 and 86) were three-fourths as active as Benadryl (342). The same compounds were prepared by the alkylation of a 1-alkyl-3(or 4)-benzylaminopyridine with a 2-halopyridine (341).

Tertiary pyrrolidylethylamine derivatives (table 41, Nos. 54-58) were synthesized via the secondary amino compounds by one of the following procedures (244):



In general, the order of activity of these pyrrolidylethylamine compounds is low. The most active members, the *p*-methoxybenzyl derivative (table 41, No.

54) and the 5-chloro-2-thenyl compound (No. 58), had an effectiveness equal to approximately one-fourth that of Pyribenzamine (244).

The pyridylarylmethanes (table 41, Nos. 96-98) were obtained from 2-benzoylpyridine and the substituted amine, using formic acid as the reducing medium (423). None of the compounds was an active histamine antagonist.

(b) Pyrimidine derivatives

The derivatives of pyrimidine are all characterized by reduced activity (RP 3015), but decreased toxicity results in most cases. The most prominent members of this group are Hetramine (table 1, No. 12; table 42, No. 3) and Neohetramine, the *p*-methoxy analog (table 1, No. 16; table 42, No. 4).

The thiényl isostere of Hetramine (table 42, No. 1), produced a compound of very low activity. Introduction of methoxy in the pyrimidine ring of Hetramine (table 42, No. 9) afforded a compound comparable to Pyribenzamine in activity and acute toxicity.

The preparations of the pyrimidines are almost identical with those of the pyridines. Aromatic aldehydes are condensed with 2-aminopyrimidine in the presence of formic acid to form the secondary amines (25, 150). An alternate method involves the treatment of 2-aminopyrimidines with sodium amide and reaction of the sodium salt with the proper halide (150). Another preparation involves condensing 2-aminopyrimidines with the corresponding chloromethyl compound in toluene, using lithium amide as the condensing agent (25).

(c) Thiophene derivatives

The pyridylthienyl compounds (table 41, Nos. 21-32, 51-53, 57, 58, 61, 65, 68, 74-77) have already been discussed. Table 14 lists other thienyl derivatives.

Diatrin (table 1, No. 9; table 43, No. 1), the phenyl analog of Thenylene, had been reported as being completely inactive by Viaud (443) (RP 2740), while Kyrides (228) reported an activity approximately two-thirds that of Antergan and Ercoli (131) claimed about equal potency and considerably lower toxicity. It was synthesized by condensing *N,N*-dimethyl-*N'*-phenylethylenediamine (prepared from aniline and dimethylaminoethyl chloride) and 2-thenyl chloride (242).

In a series of arylthiophene derivatives synthesized by Kyrides and coworkers (228, 230) (table 43, Nos. 1, 2-10, 15, 18), *N,N*-dimethyl-*N'*-(5-chloro 2-thenyl)-*N'*-phenylethylenediamine (table 43, No. 6) proved to be the most potent, approximately 125 per cent as active as Antergan in animal tests. The introduction of chlorine into the thiophene ring had a potentiating effect on antihistaminic activity, similar to that observed in the pyridine series (90). When chlorine was introduced into the phenyl ring, the activity dropped markedly (table 43, Nos. 2-4, 8, 9). The *o*-chlorophenyl derivatives (Nos. 2 and 7) had negligible activity, the *m*-chlorophenyl compounds (Nos. 3 and 8) were slightly active, and the *p*-chlorophenyl members (Nos. 4 and 9) were the most active, but the best compound in this series (No. 4) was only one-half as active as Antergan.

Introduction of a third methyl group in place of the aryl group (table 43, No.

15), or replacement of the 2-thenyl group by methoxybenzyl, practically eliminated activity. Substitution of chlorine or the 4-morpholinyl group for the dimethylamino group produced inactive compounds (230).

(d) Thiazole derivatives

Viaud (443) found the thiazolyl derivative of Neoantergan to be practically inactive (RP 2909), but Feinberg found it to be quite active (22, 137) (table 1, No. 27; table 44, No. 2).

The parent arylthiazole compound (table 44, No. 1) was synthesized by reacting benzylamine with dimethylaminoethyl chloride in the presence of potassium acetate and treating the *N*-benzyl-*N*-(2-dimethylaminoethyl)amine with 2-bromothiazole (400). It was found to possess 0.1 the activity of Neoantergan by Viaud (443) (RP 2764).

(e) Furan derivatives

The furyl isosteres of Pyribenzamine proved effective histamine antagonists. The pyridyl-substituted furans are listed in table 41 (Nos. 18-20, 50, 56), while the arylfurfuryldiamines are tabulated in table 45.

The unsubstituted furfuryl derivative, Foralamin (table 1, No. 11; table 41, No. 18), proved as effective an antagonist as Pyribenzamine when tested in guinea pigs against histamine aerosol or intravenous injection of histamine (187, 441). The bromofurfuryl derivative (No. 20) was only slightly less effective. These results are in agreement with those reported by Viaud (443) (RP 2803), but Biel (25) claimed the furyl isostere of Pyribenzamine to be twice as active. The toxicity of the furfuryl compound was the same as that of Pyribenzamine, whereas the bromofurfuryl derivative was approximately 50 per cent less toxic (441).

In a general study of the pharmaceutical applications of furan derivatives, Hayes and coworkers (187) prepared the two aforementioned derivatives plus the chloro- and methyl-furfuryl compounds (table 41, Nos. 19 and 50). The latter was practically inactive, while the 5-chloro member had approximately one-half the activity of the bromo compound. In contrast to the report of Vaughan and Anderson (441), the acute toxicity of the furfuryl derivative (as the fumarate salt) was observed to be approximately two-thirds the toxicity of Pyribenzamine.

Methoxy or isopropyl substitution in the para position of the phenyl ring of the furyl isostere of Antergan (table 45, Nos. 2 and 3) resulted in appreciable lowering of activity, coupled with an increase of acute toxicity in the case of the isopropyl derivative (25).

Foralamin (table 41, No. 18) was synthesized by an initial reaction of 5-bromo-furfuryl alcohol with thionyl chloride in toluene solution at low temperature. The unstable intermediate furfuryl chlorides were treated directly with the sodium salt of *N,N*-dimethyl-*N'*-(2-pyridyl)ethylenediamine (441). The lithium salt of the latter has been employed (229), as has been lithium amide for the condensation (25). Hayes and coworkers (187) condensed furfural or 5-halo-2-furaldehydes with 2-aminopyridine to yield the azomethines. The latter were

catalytically hydrogenated to yield the *N*-furylmethyl-2-aminopyridines. The Schiff bases were either reductively alkylated with a Grignard reagent or lithiated with lithium amide in benzene and treated with 2-dimethylaminoethyl chloride to yield the desired base.

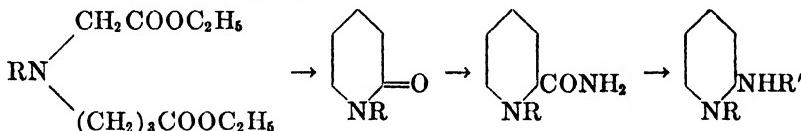
(f) Piperidine and pyrrolidine derivatives

These groups are usually met as part of the side chain in the replacement of the usual $-\text{N}(\text{CH}_3)_2$; however, molecular species have been prepared in which these nitrogen heterocycles are in the "front" of the structure.

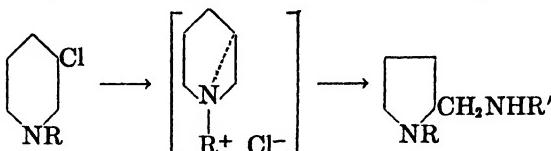
The 4-aminopiperidines containing isocyclic (table 36) and pyridyl moieties (table 41, Nos. 85 and 86) have been discussed. *N*-Benzyl-*N*-4-piperidylethyl-*N'*-pyrrolidylethylamine (table 46, No. 6) was prepared from pyrrolidylethylamine (obtained by catalytic reduction of pyrrolidylacetonitrile), which was condensed with benzyl-1-alkyl-4-piperidine in toluene solution with potassium carbonate and copper powder catalysts (342).

N-Substituted piperidines without any nuclear substitution (table 46, Nos. 1-3) and the piperidone (No. 4) were all inactive.

The replacement of the ethylenediamine unit by a 3-aminopiperidine group was shown to yield weakly active compounds (341, 343) (table 41, Nos. 80-84). They were synthesized through reductive alkylation of amines with 1-alkyl-3-piperidones. 1-Methyl- and 1-ethyl-3-piperidone were prepared from the alkylaminodicarboxylic esters (343).



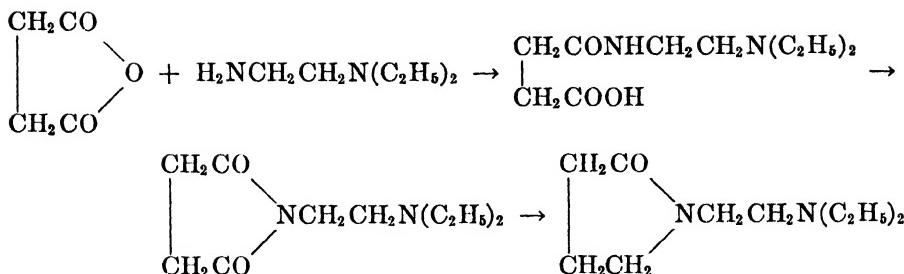
2-Aminomethylpyrrolidines resulted from a novel rearrangement of the piperidine ring. Treatment of 1-ethyl-3-chloropiperidine with benzylamine did not give the expected 3-benzylaminopiperidine; instead, 2-aminomethylpyrrolidines were obtained. Since 1,2-chloroamines react as though an intermediate cyclic imonium salt is formed, the formation of a similar intermediate from 3-chloropiperidine would explain the formation of 2-aminomethylpyrrolidines.



The direction of the imonium ring opening is dependent upon the nature of the attacking nucleophilic agent, and a strongly basic group evidently favors the formation of the pyrrolidine structure (339).

(g) Pyrrolidone, pyrazine, and pyridazine derivatives

Pyrrolidones (table 47, Nos. 1 and 2), prepared recently in Japan, were inactive (307). Succinic anhydride and diethylethylenediamine yielded the succinamide, which on electrolytic reduction produced 1,2-(diethylaminoethyl)-2-pyrrolidone.



The pyrazine (table 47, No. 3) and the pyridazine were very weak antagonists.

(h) Imidazole and imidazoline derivatives

In a study of imidazole compounds resembling histamine in structure, 4-methylimidazole, 4-ethylimidazole, and related compounds were synthesized (196, 432) (table 48). Some of the 4-(substituted aminomethyl)imidazoles showed a weak antihistaminic action, while others imitated histamine.

4-(Benzylphenylaminomethyl)imidazole (No. 9) is of interest because it is a position isomer of 2-(benzylphenylaminomethyl)imidazoline (Antistine, table 1, No. 2). The imidazole possesses about one-half the antihistaminic action of Antistine.

In the ethyl series, antihistamine activity was shown by No. 25, which possessed 0.5 of the activity of Pyribenzamine. The rest of the compounds in table 48 displayed various degrees of histamine-like activity.

The thiophene analog of Antistine (table 49, No. 1) had approximately 5 per cent of the activity of Antergan (228), while the tetrahydropyrimidine analog (No. 2) possessed insignificant activity (230).

A brief study was made by Turner of substances containing the imidazole nucleus (Nos. 3-6). None had any antihistaminic activity (431).

Jones (214, 215, 216) synthesized a series of 2-substituted imidazoles and 3- and 4-substituted pyrazoles in a broad study of the possible relationships of chemical structure to biological activity. None of the compounds are histamine antagonists, but rather resemble histamine in action. An excellent concise table correlating the structure of 2-aminoethyl heterocyclic nitrogen compounds and histamine activity was drawn up by Lee and Jones (468).

b. N-Polyyclic derivatives of ethylenediamine

Modifications of the linkages between the aryl groups in the Antergan molecule were of little avail (*cf.* tables 24 and 25). The diphenylamine derivative, RP 2565 (table 25, No. 3), had only about 1/50th the activity of Antergan. Polycyclic derivatives, such as carbazoles and phenoxazines (tables 50 and 53), possessed slight activity. A search for antimalarials among the phenothiazines and their testing as antihistamines led to the discovery of extreme potency in a bridged structure (178, 181).

By far the most active antihistaminic compounds known belong to the series of phenothiazines or thiadiphenylamines, which have been thoroughly investi-

gated by the Rhône-Poulenc research group. Only in this series and in the acridines have especially potent antagonists been found.

The potency of the active phenothiazines (RP 3015, RP 3277) is about fifteen times that of Pyribenzamine and the duration of action is three times that of Antergan or Pyribenzamine.

(1) Rhône-Poulenc *N*-polycyclic diamines

Table 50 lists the various polycyclic derivatives prepared for testing as histamine antagonists by Charpentier and described by Viaud (443) of the Rhône-Poulenc laboratories. The latter noted that the 3-aminoquinolyl derivative (RP 2970) was inactive. In the phenothiazine series, the dimethylaminoethyl side chain (RP 3015) gave antiasthma activity similar to that of Antergan, but considerably higher protection against intravenous histamine. While 20 mg./kg. of Antergan protected against 120 lethal doses, a similar dosage of RP 3015 protected against 700 lethal doses. Branching of the side chain by adding one methyl group (RP 3277, RP 3389) yielded further improvement. However, two other branched-chain compounds having two methyl groups (RP 3300, RP 3349) were completely inactive. Both the diethyl analog of RP 3015 (RP 2987) and the trimethylene analog (RP 3276) were almost inactive. When methoxyl groups were introduced into the phenothiazine nucleus (RP 3298, RP 3299), no particular advantage accrued.

Replacement of the phenothiazine molecule by related nuclei led only to compounds of inferior activity (RP 3283, 3289, 3040, 3041, 3192, 3390, 3398). Variations within this group of compounds, such as the formation of the sulfoxide (RP 3283) and the sulfone (RP 3289), led to the interesting observation that the sulfoxide was inactive, while the sulfone was as active as Antergan. The most active antagonist in the series was RP 3277 or Phenergan (table 1, compound 18), which is able to protect guinea pigs against 1500 lethal doses of histamine (181). These high doses led shortly afterwards to death, due to perforating stomach ulcers (180).

(2) Individual polycyclic groupings

(a) Phenothiazines

Charpentier (77, 394) prepared RP 3015 (table 51, No. 1) by reacting phenothiazine with dimethylaminoethyl chloride in the presence of an agent binding halogen acid, preferably sodium amide. The diethyl analog had been prepared, for other purposes, by Gilman and Shirley (162), by condensing phenothiazine with 2-chloroethyl *p*-toluenesulfonate in the presence of butyllithium and reacting the 10-chloroethylphenothiazine with dimethylamine in the presence of copper powder. The diethyl compound (Diparcol) was found to be useful in the treatment of Parkinsonism.

The quaternary ammonium salts (table 51, Nos. 31-39) were prepared by heating the tertiary base with the appropriate alkylene dihalides (78). The 8-chlorotheophylline salt of RP 3015 has been described as extremely potent (91, 146, 157, 317).

In the series of *N*-(pyrrolidylalkyl)phenothiazines (table 51, Nos. 17-22), *N*-pyrrolidylethylphenothiazine (No. 17; Pyrrolazote, table 1, No. 20) showed the highest level of antihistaminic activity (338). They were synthesized by hydrogenating pyrrole and its dimethyl homologs over Raney nickel and treating the resulting pyrrolidines with the appropriate alkylene chlorohydrin. The *N*-pyrrolidylalkanols thus formed were converted into the corresponding *N*-pyrrolidylalkyl chlorides with thionyl chloride. *N*-Alkylation of phenothiazine with the chlorides in the presence of sodium amide proceeded smoothly (198, 199, 338).

The *N'*-(2-hydroxyethyl)-*N'*-methyl derivative (table 51, No. 7) appears to possess about 1.5 times the activity of Benadryl (99).

The acylphenothiazine derivatives (table 51, Nos. 8-16) have weak antihistaminic power. They were prepared by heating phenothiazine with an excess of the appropriate haloacyl halide (126).

Miescher (286) described the imidazolyl derivative (No. 25) and the 2-methoxy compound (No. 28), prepared from the thiadiphenylamine and 2-chloromethyl-2-imidazoline, or from 10-(cyanomethyl)phenothiazine and ethylenediamine. No activity data are given.

An extensive series of *N*-(dialkylaminoalkyl)phenothiazines (table 52) were synthesized by Wright and coworkers (464). The pharmacological results (table 52) demonstrated that the introduction of groups larger than methyl on the terminal amino nitrogen does not increase the antihistamine effectiveness; more often the activity is lowered (464).

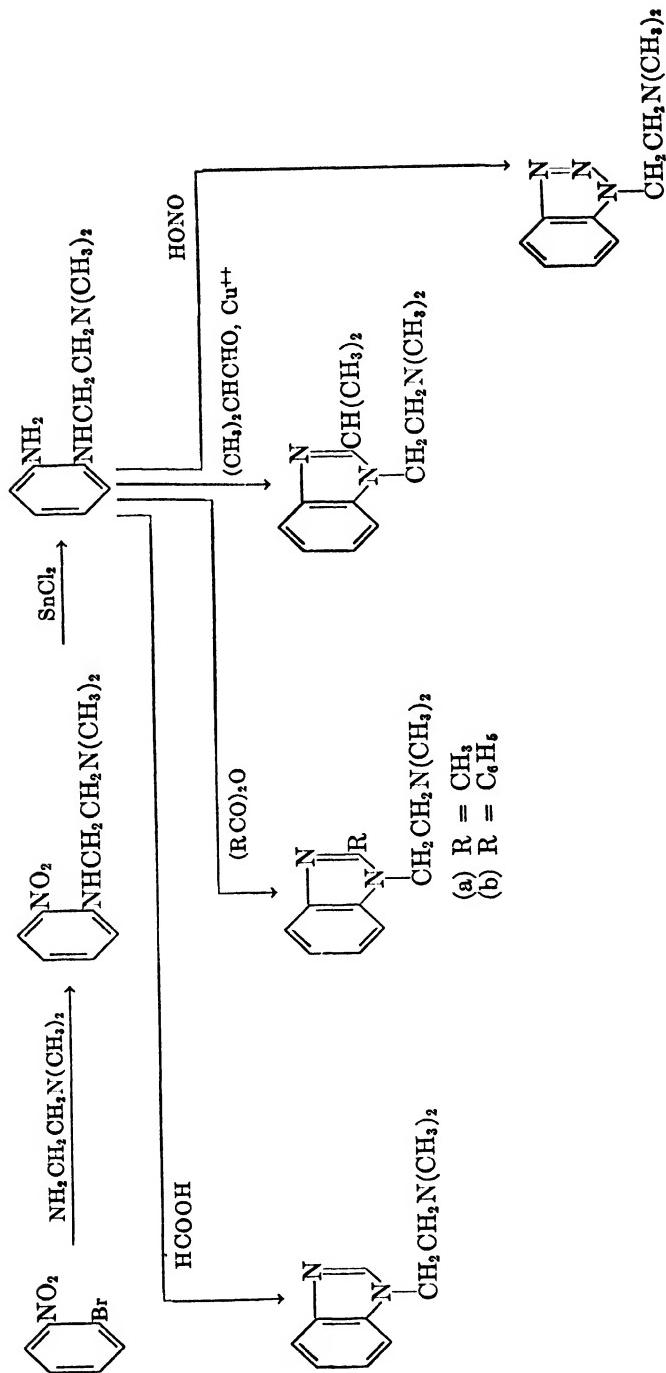
(b) Polycyclic functions other than phenothiazines

The indole and carbazole derivatives (table 53, Nos. 1-5, 39-41) were prepared by heating the appropriate sodium salts with the dialkylaminoethyl chloride. The compounds possess weak to moderate antihistaminic activity. 1-[2-(1-Pyrrolidyl)ethyl]indoline (No. 2) and the phenylindole (No. 3) had 0.1-0.01 the spasmolytic activity of Benadryl, while the phenylindolines (Nos. 4 and 5) had about one-half the activity. The carbazole and tetrahydrocarbazole (Nos. 39 and 40) were 0.1-0.01 as active and the hexahydro derivative possessed one-third to one-sixth the activity of Benadryl (460). The dimethylaminoethyl carbazole derivative (No. 36) was practically inactive (52).

Benzimidazole derivatives (Nos. 6-9) appeared to be of interest because they have the —N—C=N— grouping present in Pyribenzamine and other agents, as well as structures analogous to the imidazole ring of histamine (461).

The benzimidazole derivatives and the benzotriazole (No. 10) were prepared from *o*-(2-dimethylaminoethylamino)nitrobenzene. Reduction with stannous chloride gave a diamine which, upon treatment with formic acid, acetic anhydride, benzoic anhydride, isobutyraldehyde, and cupric acetate and nitrous acid gave the respective benzimidazole and benzotriazole derivatives (461, 462) (see page 353). These compounds possess only slight antihistaminic activity.

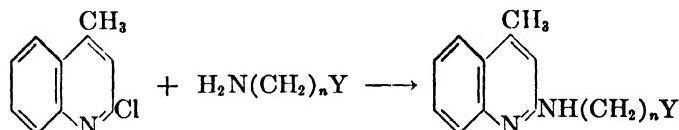
The quinoline derivatives (Nos. 13-20) are all practically inactive, agreeing with the results of Viaud (443), who found RP 2756 inactive. The lack of activity in Nos. 11, 12, 14-18 suggested that the presence of at least one aromatic nucleus



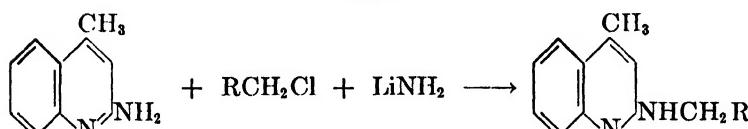
or its isostere is desirable for potency (307), but the furyl and thenyl derivatives (Nos. 19 and 20) possessed about 0.01 the activity of Pyribenzamine (244). The lepidyl-substituted diamines (Nos. 21-34) seem to be mildly active (5, 220).

The intermediate 2-lepidyl secondary amines were prepared either by heating 2-chlorolepidine with excess alkylenediamine (method A) or treating 2-lepidylamine with a halide in the presence of lithium amide (method B). An alternate method involved condensation of the aminolepidine with benzaldehyde, using formic acid as a solvent, and reduction (method C). The tertiary amines were prepared by standard procedures (methods D and E) (220).

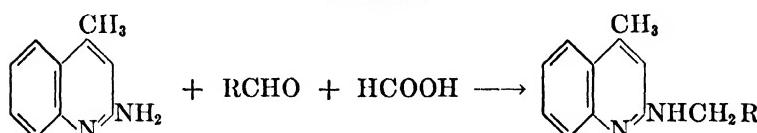
Method A



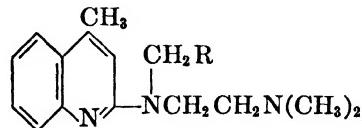
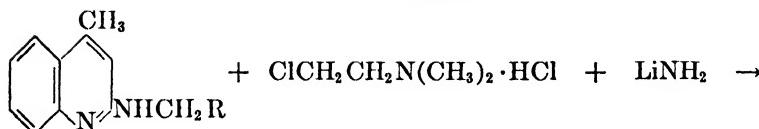
Method B



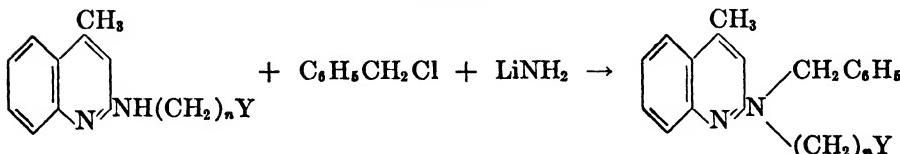
Method C



Method D

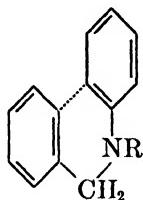


Method E



The quinoxaline derivative (No. 35) was synthesized by condensing dimethylaminoethyl chloride with *N*-benzylbenzamide to give *N*-benzoyl-*N*-benzyl-*N'*,*N'*-dimethylethylenediamine, which was hydrolyzed to the benzyl derivative. This was condensed with 2-chloroquinoxaline to form the desired compound. No pharmacological data were given (156).

Huttrer (202) noted that the 5,6-dihydrophenanthridine derivatives (Nos. 42-45) differed from the Antergan type compounds only in the existence of the linkage represented by the dotted line.



Nos. 42 and 45 were completely inactive, while No. 43 had very slight activity (202). It thus appears that ring closure does not aid in the antihistamine field, as it does with antispasmodics (e.g., Trasentin and Pavatrine).

The acidine derivative (No. 47) is an extremely potent antagonist, possessing variously 7.5 times the activity of Benadryl (290) or 16 times the potency (146). It appears too toxic for clinical usage (95, 146), though claims for low toxicity have been made (290).

3. Conclusions

Table 54 represents a compilation by Scholz (384) which illustrates lucidly the relationships between structure and activity in the ethylenediamine derivatives. Even though exceptions exist, one can conclude from the experimental findings that in order to get active compounds both nitrogen atoms of the ethylenediamine moiety should be completely substituted with organic radicals. For highest activity one nitrogen usually should be dimethylated and the other should carry an aryl radical and an aralkyl radical.

As far as the aryl radical is concerned maximum effect has been observed with α -pyridyl; phenyl, β - or γ -pyridyl, picolyls, pyrimidyl, thiazolyl, etc. show less activity. In the case of the aralkyl radical, the alkyl chain should be a methylene group, whereas the aryl part may be phenyl, substituted phenyl, furyl, thiienyl, substituted thiienyls, thiazolyl, etc. Substitution of a propylene or a branched-chain alkylene radical for the ethylene portion results, in most cases, in lowered effectiveness (384). The fusion of the aryl and aralkyl portions into a polycyclic ring is only effective in the case of the thiodiphenylamines, where the branching of the side chain plays an important role which is lacking in the other series.

In the ether series, substituents on the benzene nucleus play a part which does not have any significance in the aniline compounds. Indeed, the *p*-methoxy group has a great importance when attached to the benzyl group of Neoantergan but is of no importance if present in the benzyl group of Antergan.

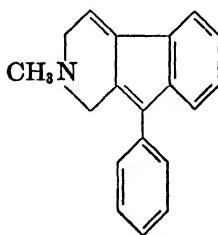
Bovet (32) stresses the significant fact that antihistaminic activity could always be detected in those substances which are structurally related to adrenolytic or spasmolytic compounds. It should again be emphasized that the compound with the highest activity is not always so superior in clinical trials.

C. DERIVATIVES OF PYRIDINDENE

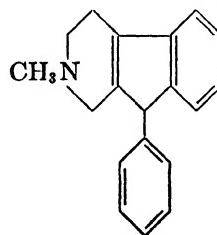
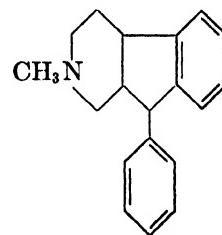
A class of compounds seemingly unrelated to the ethylenediamines is that of the derivatives of pyridindene (indenopyridine), which contain the novel fusion of the indene and pyridine rings.



From a number of pyridindenes (table 55), 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (Thephorin; table 1, No. 25; table 55, No. 9) showed promising antihistamine activity. In a study of three derivatives of pyridindene which differed only in the number of double bonds, the dihydro (Nu 1326), tetrahydro (Nu 1504), and hexahydro (Nu 1525), Lehmann (237) concluded that Thephorin (Nu 1504) was about one-half as effective as Pyribenzamine in



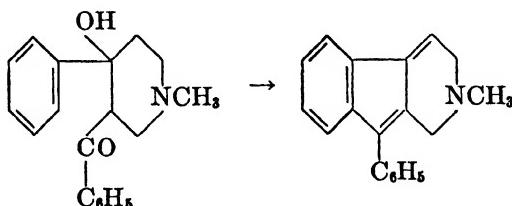
Nu 1326

Thephorin
Nu 1504

Nu 1525

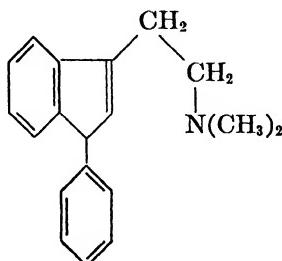
aerosol testing and protection against intracardially injected histamine. Of the two other derivatives, Nu 1326 only showed some antihistamine activity, showing that double bond changes cause striking decreases in activity.

The pyridindenes or 1*H*-indeno[2,1-*c*]pyridines result from the cyclodehydration of 1,3,4-trisubstituted piperidines by heating with strong hydrobromic or sulfuric acid. Thus, 2-methyl-9-phenyl-2,3-dihydro-1*H*-pyridindene is produced from 3-benzoyl-4-hydroxy-1-methyl-4-phenylpiperidine (319, 320).



Treatment of Mannich products, such as $C_6H_5COCH_2CH_2NRCH_2CH_2COC_6H_5$, with hydrobromic acid gives initially the piperidine derivative, which undergoes further cyclization to the above pyridindene derivative (319). Thus, derivatives of dihydro-1-pyridindenes have become one of the most easily accessible classes of polynuclear heterocyclic compounds.

The pyridindenes are placed immediately after the ethylenediamine derivatives, since Thephorin can be interpreted as a substance in which the aliphatic side chain $-CH_2CH_2N(CH_3)_2$ has participated in ring closure, somewhat similar to the imidazoline side chain of Antistine (201). The relationship is shown in the open-ring analog of Thephorin.



D. DERIVATIVES OF AMINOPROPANE

Dialkylaminopropanes

Two groups, one working at the Burroughs Wellcome Research Laboratories in Kent, England (1, 2), and the other at the laboratory of the Schering Corporation in Bloomfield, New Jersey (429, 231), investigated the effect of replacement of the oxygen and nitrogen functions in the ethanolamine and ethylenediamine derivatives by a methylene group to yield *C*-substituted dialkylaminoalkanes (tables 56, 57, 58).

The United States group announced the effectiveness of 3-phenyl-3-(2-pyridyl)-*N,N*-dimethylpropylamine (Trimeton, table 1, No. 26), which was estimated to possess four times the therapeutic index (effective dose/toxicity) of Pyribenzamine (427).

Chlorination of Trimeton in the phenyl ring produced a twentyfold increase in potency, yielding Chlortrimeton (table 1, No. 7), which appears to be the most potent oral antihistamine known. Halogenation produced no appreciable change in toxicity.

Tislow (426) has discussed the effect of halogenation on antihistamine activity. The tremendous change in Trimeton has been noted. However, halogenation does not always produce more potent compounds. Chlorobenzhydryl ethers (table 6, Nos. 63-68) are listed without any pharmacological data. Chlordecapryyn (table 14, No. 20) does not appear to be more active than the parent compound. Chlorination of the phenyl group in the benzhydrylpiperazines (table 33, No. 6) gave increased potency and lengthened duration of action. The *p*-chloro derivative of Pyribenzamine (table 41, No. 8) appears to be slightly more potent than the parent compound. The fluoro analog (table 41, No. 7) is

more active than the chloro, while the bromo compound (table 41, No. 10) is slightly less active. Halogenation of the 2-thenyl groups in Thenylene or Histadyl gave three times the activity of the unsubstituted compound (table 41, Nos. 24 and 25). In the 3-thenyl series, halogenation did not produce the desired effect (table 41, Nos. 28, 30, and 31), achieved in 2-thenyl isosteres. The bromofurfuryl derivative (table 41, No. 20) was slightly less effective than the unsubstituted derivative.

The propylamines were prepared by the condensation of 2-tertiary aminoethyl halides with (2-pyridyl)benzyl cyanide and subsequent removal of the cyano group or alkylation of the appropriately substituted dihydrostilbazoles with dialkylaminoalkyl halides (404, 406).

Unaware of the work at the Schering laboratory, Adamson (1, 2) prepared a large series of aminoalkyl tertiary carbinols, esters, propenes, and propanes (table 56). Several of the 3-tertiary-amino-1,1-diphenyl-1-propenes and -propanes exerted a moderate antihistamine action, in addition to surface anesthetic, spasmolytic, and mydriatic properties.

Since the replacement of the *N*-phenyl ring of Antergan by the 2-pyridyl group of Pyribenzamine and others increased the potency, it was sought to increase the antihistamine potency of the substituted allylamines by replacing one of the phenyl rings by 2-pyridyl (table 57) (2).

The aminopropanols were prepared by treating the appropriate aryl-2-tertiary-aminoethyl ketones (prepared by the Mannich reaction) with 2-pyridyllithium, and were converted into water-soluble neutral oxalates for pharmacological testing. The pyridylecarbinols, in contrast to the analogous diphenylecarbinols, were resistant to moderately severe dehydration conditions. This relative stability is in accord with the electrophilic nature of the 2-pyridyl group. Dehydration to the 1-propenes was effected by heating with aqueous sulfuric acid.

The activities of the carbinols were nil. The allylamines, like the propylamines, were outstanding for their antihistamine activity. The influence of the tertiary-amino substituent did not appear to run parallel in the two series. In the allylamine series, the pyrrolidino group had the most favorable effect, while in the propylamine series the highest activity is found in the dimethylamino compounds, as in Chlortrimeton.

In a series of bridged-ring propylamine hydrochlorides and 8-chlorotheophyllinates (table 58), the most active compounds were the thioxanthene (No. 2) and the dihydroanthracene derivatives (No. 5) (95, 146, 317).

In view of the similarity in the pharmacological properties between the ethyldialkylamines and the 2-imidazoline derivatives (*cf.* tables 6 and 11), a series of amidine and dihydroglyoxaline analogs of 3,3-diphenylpropylamines were prepared (212). This group of compounds is characterized by 3,3-diphenyl-*N,N*-dimethylpropylamine (Aspasan, table 58, No. 7), which had been prepared for testing as an antispasmodic and analgesic (28, 29). Aspasan possessed 0.1 the activity of Benadryl. The imidazoline analog of Aspasan (table 59, No. 1) was obtained from 2,2-diphenylpropionitrile either through the imidate hydrochloride (224) or by fusion with 2-aminoethylammonium toluene-*p*-sul-

fonate (309). The amidines (Nos. 2-4) were prepared by the action of an excess of ammonia or of the appropriate amine on ethyl 2,2-diphenylpropionimidate hydrochloride. For comparison diphenylacetamidine (No. 5) and 2-benzhydryl-2-imidazoline (No. 6) were prepared by standard methods. Only 2,2-diphenylpropionamidine (No. 3) had approximately one-tenth the activity of Benadryl.

The benzylimidazoline (No. 7), 1-naphthalenemethyl (No. 8), and biphenyl (No. 10) derivatives were prepared from the arylacetamide and excess ethylenediamine (283).

E. DERIVATIVES OF BUTENE AND STILBENE

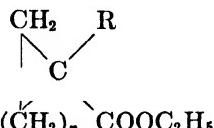
The antihistamine activity of basic propenes has already been discussed (tables 56 and 57). A series of 3-tertiary-amino-1,1-(2-thienyl)-1-butenes (table 60) has recently been announced (3), which exhibit considerable antihistaminic, spasmolytic, local anesthetic, and particularly analgesic activity. The butenes were prepared by the action of 2-thienyllithium on the appropriate ethyl 2-aminobutyrate.

Basic stilbenes, synthesized by Rohrmann (*cf.* 344), are unusual in that maximum activity (twice that of Benadryl) is obtained with a piperidinoethyl side chain (Lilly 01003, table 1, No. 14). The substitution of a dimethylamino group for the piperidino function cuts the activity in half.

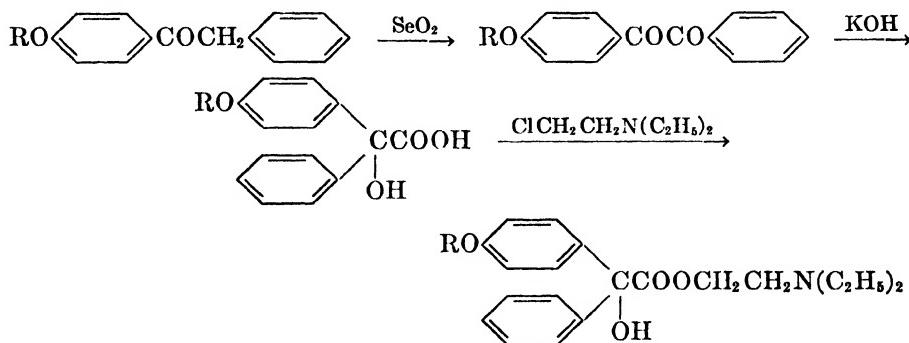
F. DERIVATIVES OF AMINOPROPIONIC ACID

Basic esters of alicyclic and heterocyclic acids have been tested as histamine antagonists, but usually this evaluation is adjunct to investigations of antispasmodic and anesthetic properties. Many of these early compounds (prior to about 1942) were tested against histamine, but cannot be mentioned here.

Tilford and coworkers (424, 440) synthesized a series of amino esters of substituted cycloalkanecarboxylic acids (table 61) for antihistamine and antispasmodic testing. No definite conclusions can be drawn in regard to relationship between structure and activity. However, a cyclohexyl or benzyl group in the 1- or 2-position of the cyclohexane ring was the most active of the series, but even the most active compound (No. 7) was less than one-half as active as Benadryl. The compounds were more effective as antispasmodics. The amino esters were prepared from the corresponding cyanides. Thus, phenylacetonitrile was condensed with an alkylene dihalide using two equivalents of sodium amide in a mixture of liquid ammonia and ether at low temperatures. Alcoholytic of the substituted nitriles by a sulfuric acid-ethanol mixture resulted in crude ethyl esters which were reesterified with the desired amino alcohol in toluene, using sodium as a catalyst.

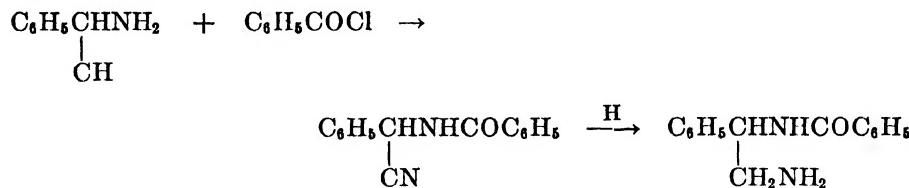


A study of diethylaminoethyl 4-alkoxybenzilates, primarily investigated for local anesthetic and antispasmodic action, yielded compounds of minor anti-histamine activity (30) (table 62). The esters were obtained from appropriately substituted desoxybenzoins by the following route:



A peak activity is reached with the *n*-amoxy derivative (No. 8), with a potency equal to that of the unsubstituted benzilate.

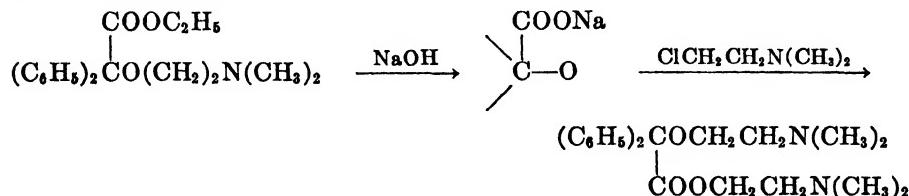
Funke and Kornmann (154) prepared a long series of ester derivatives of ethylenediamine by condensing arylaminonitriles with arylacyl halides to give the arylbenzamidoacetonitriles, which were reduced over Raney nickel to give the ethylenediamines.



The amines are not described as antihistamines, but could be valuable in the preparation of antagonists.

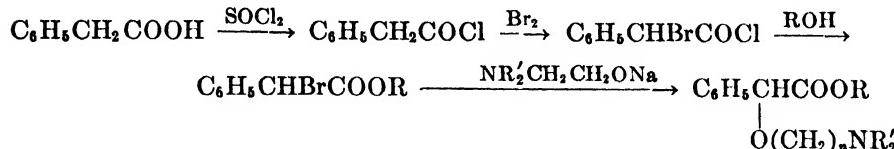
In a study of the comparative spasmolytic activities of benzhydryl alkamine ethers, Alles and Redemann (6) (cf. page 319, table 6A) noted that keto and ester compounds of essentially the same molecular size as the dialkylaminoethyl benzhydryl ethers are relatively much less active in their antihistamine activities and no more active in their antiacetylcholine activities (table 63, Nos. 1-3).

Ether-esters of hydroxydiphenylacetic acid were prepared, for testing, by treating a dialkylaminoalkyl halide with an alkali metal derivative of an ester (table 63, Nos. 4 and 5) (294, 295).



The replacement of one of the benzene rings of the Benadryl molecule (table 1, No. 3) with various ester groups and altering the structure of the dialkylamino-alkyl group yielded compounds of negligible activity (table 64) (429).

The esters, derivatives of phenylacetic acid, were prepared as shown by the following continuous equation:

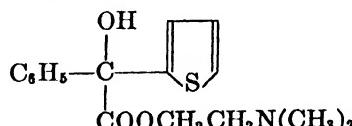


Ethers of 2-hydroxypyridine were investigated to ascertain the effect of introducing the 2-pyridyl group into compounds for possible antihistaminic and antispasmodic action (190). The 2-pyridylaryl ethers were prepared by heating 2-bromopyridine and the phenol in the presence of anhydrous potassium carbonate. Where this method was inapplicable, the compounds were synthesized by heating the appropriate dry sodium phenoxide with 2-bromopyridine in the presence of copper powder. The 2-pyridyl ethers of ethyl glycolate, ethyl lactate, and ethyl mandelate were prepared through interaction of the sodium alkoxide of the ester with an excess of 2-bromopyridine. When applied to ethyl benzilate, this method failed, but the ethyl diphenyl(2-pyridoxy)acetate was prepared by heating dry sodium benzhydrolate with 2-bromopyridine and copper powder. The esters were converted to the alkamine esters of 2-diethylaminoethanol and 3-diethylamino-1-propanol through alcoholysis of the alkyl esters with excess amino alcohol containing a small quantity of dissolved sodium metal (table 65). Pharmacological evaluation was not given (190).

A series of esters of bridged compounds were prepared in 1942 by Burtner and Cusic (53-56) and tested by Lehmann and Knoefel (239, 240, 241) to determine the influence of the bridge on physiological activity (table 66). It was found that the replacement of the C-C (fluorene, No. 1) bridge by —CH₂— (dihydro-anthracene, No. 2) led to much stronger antihistaminic activity, while substitution of the —CH₂— by oxygen (xanthene, No. 4) caused greater spasmolytic potency, and the substitution of sulfur (thioxanthene, No. 5) for the oxygen caused lesser activity. Substitution by an imino group (acridine, No. 4) reduced the histamine antagonism.

The 2-diethylaminoethyl fluoresene-9-carboxylate was prepared from fluoresene-carboxylic acid and diethylaminoethyl chloride, while the dihydroanthracene derivative was made from 9,10-dihydroanthracene-9-carboxylate and the diethylaminoethyl chloride. The carboxylic acids were prepared by carbonation of the lithium derivatives of the hydrocarbons.

Within a series of esters of phenyl- α -thienylglycolic acid, the dimethylamino derivative was reported to have some activity (467). The piperidine analog was



one-half as active as Benadryl against histamine (79). However, it was quite toxic and produced convulsions.

V. SUMMARY AND GENERAL CONCLUSIONS

An attempt has been made to present most of the salient facts relative to the chemistry of the present antihistamine agents. The search for the pharmacological and clinical results of the well-known antihistaminics, which have had wide usage, were not included here, since these data are excellently covered in several papers (*cf.* page 309), notably in the annual reviews, entitled "Progress in Allergy," which are published in the *Annals of Allergy*.

The following conclusions as to correlation of structure and chemotherapeutic activity are based on such scanty and variable pharmacological data that they are of little scientific value. They are offered as a guide to future research, and not as a sign that negative conclusions invalidate further work.

The basic unit for all effective agents has been the ethylamine skeleton. Essentially all the compounds contain this group, whether it be a "straight-chain" compound such as Antergan or part of a ring compound such as Antistine. Thus such widely differing (structurally) compounds as Thephorin, Antistine, Perazil, Trimeton, and Phenergan show a common factor. It is interesting that the ethylamine skeleton also corresponds to the side chain of the histamine molecule and to part of the imidazole chain.

With the exception of the 2-methyl-2-imidazoline side chain, the terminal nitrogen should be a tertiary nitrogen, for secondary and primary amino derivatives are inactive. It is interesting that while the *N*-diethylalkyl group seems characteristic of antispasmodic compounds, the *N*-dimethylalkyl group appears to be the optimal grouping in the antihistamine compounds. Branching of the side chain, with methyl attached to the α -carbon, seems to have had a beneficial effect, but β -methyl substituents sharply reduce activity. Larger alkyl groups cause decreased activity (tables 5 and 52). When the methyl groups are part of a heterocyclic side chain, such as pyrrolidino, piperidino, and morpholino, less active compounds are usually produced, although the pyrrolidine derivatives in the benzhydryl ethers and phenothiazines have been reported to possess at least as great activity as the dimethyl analogs. No such effect was noted in the *N*-pyridyl series (*cf.* table 41, Nos. 54-58). The methylpiperazyl ether is also a decided improvement. Substitutions in the pyrrolidyl portions of the pyrrolidinopheno-thiazines (table 51, Nos. 17-22) were of no advantage.

An increase in side-chain length from ethylene to trimethylene or greater has usually produced a sharp drop in activity. Quaternization in the ethers has led to decreased antihistaminic activity but increased antispasmodic activity (*cf.* page 320 and table 32). There is sometimes a notable difference in potency of the various salts of a particular compound. This is probably due to increased solubility or absorption in the animal. Thus, Chlortrimeton maleate appears more active than the hydrochloride. Various dicarboxylic acid salts, such as the acid succinates, fumarates, malates, citrates, acid tartrates, and maleates have been found suitable.

The nucleus of all the antihistaminic agents should have a minimum of two

aryl or aralkyl groups or their equivalent in a polycyclic ring system. Monoaryls, such as the phenoxyethyl ethers (table 3), triazines (tables 20, 39), Fournau amines (table 22), and imidazoles (table 48), were all weak antagonists. A minimum molecular weight of about 150 seems necessary.

Ether linkages on the carbon of the basic ethylamine skeleton appear to lead to relatively more toxic and sedative properties, although the groups attached to the ether oxygen exert severe modifying effects. Thus, Benadryl is less toxic than F 929 and Decapryl, while the benzylphenols are more potent and much less toxic than any of these. The great increases in potency found in the diamines by replacement of alicyclic by heterocyclic groups were noted, but the effect was not as great as in the ethers. Substitution in the aryl groups has yielded some improvement in the benzhydryl ethers. The phenoxyethyl ethers have to be substituted in the ring for any adequate activity. Trisubstitution in the nuclei was disadvantageous, for the 2-dimethylaminoethyl triphenylmethyl ether was practically inactive. Diheterocyclic substitution in the ether nuclei led to inactive compounds, as did hydrogenated rings (*cf.* table 15). It is interesting that the benzyl group does not have the same favorable effect with the pyridyl-substituted ethers (table 14, No. 11) as with the diamines, nor does *p*-methoxy substitution help (*cf.* page 316 and table 11). Peroxides, such as the dioxolanes (table 12), were quite weak.

The effect of halogenation has been discussed (*cf.* page 357). Isoteric principles have been effectively used, for the replacement of the aryl group by thenyl and furfuryl in the pyridyl series (table 41) has left essentially the same activity. The same did not seem to apply to the pyrimidine-aryls (*cf.* page 347). The addition of the benzyl radical increased the basicity and the activity. *p*-Methoxy substitution in the benzyl radical improved the pharmacological activity in Neoantergan. However, clinically, there is often little difference between the action of Neoantergan and that of Pyribenzamine. The substitution of the pyrimidyl group in the diamines lowers the potency but also reduces the toxicity. Clinically, Neohetramine is not as potent as other drugs, but it also has fewer side actions. The aminopropane derivatives, such as Trimeton, are not as active pharmacologically or clinically. However, Trimeton is also neither as toxic nor as likely to cause drowsiness. The *p*-chloro derivative is extremely active and has no increased toxicity.

Thephorin, a pyridindene derivative, is as effective as most of the previous drugs. Its greatest advantage is that it enervates, rather than sedates, the patient.

Attempts to correlate physical properties with chemotherapeutic activity have been rare. Baltzly and coworkers (16) suggested that the prolonged action of Perazil (*cf.* page 338) might be due to inhibition of metabolic oxidation, and that the electron-releasing or -attracting effect of the polar *p*-halogen groups ought to be reflected in the pK_a values. Certain trends were noted in the compounds of table 33, although the effects of variations on the basicity of the benzhydrylamino nitrogen tend to be masked by the presence of the more strongly basic methylamino group.

The influence of methoxy substitution on the pK_a was less than expected. The resonance of a methoxyl group could be expected to increase electron con-

centration para to itself and thus increase basicity. This tendency seems of minor importance here, and the methoxyl group seems to function mainly through its inductive action, electron attraction being dominant. This suggests that the methoxyl resonance, while important in activated or transition states, has little influence on continuing unactivated properties of the molecule. Yet it is evident that the nucleus of antihistamine agents must include an unsaturated ring structure attached to oxygen, nitrogen, or carbon in such a way as to allow resonance stabilization of the active intermediate, for all compounds with saturated substituents are practically inactive. Substitutions on the aromatic rings themselves which interfere with, but probably would not completely prevent, stabilization through hyperconjugation usually cause relative inactivation. Methyl substitutions in the 4- and 2-positions have not increased potency, but in the 3-position (Toladryl), where it would not interfere with conjugation, there appears to be a favorable effect. It is probable that steric forces are added factors in the reduced activity of ortho-substituted compounds. The extra potency of benzyl compounds and similar methylene separations between the aromatic rings and nitrogen lends support to resonance ideas, for direct apposition of the ring and the nitrogen, which would reduce but not prevent stabilization, yields lowered activity. The interposition of one carbon atom permits effective resonance. The replacement of the benzyl group in Antergan by heterocyclic functions yielded little improvement, but change of the phenyl group caused great changes. Two-carbon interposition between the aryl group and nitrogen reduces activity, possibly owing to inhibition of resonance. The phenoxyethyl derivatives which favor hyperconjugation are improved in the benzhydryl series, where the stability of the ion decreases with the increase of aromatic rings. The sharp differences in the dimethyl and diethyl derivatives could not be expected on the basis of resonance; possibly planarity is involved. The possible anomaly in the case of the *p*-halogen derivatives may lie in that these antihistaminics function by being absorbed on some enzyme whose matrix admits the presence of para substituents only (16).

No correlations can be drawn between activity and the intrinsic chemical properties of the aromatic nuclei. The pyridine, pyrimidine, pyrazine, pyridazine, and certain of the bridged-ring systems are relatively weakly nucleophilic, while the thienyl, imidazolyl, and phenyl systems are relatively strongly nucleophilic. All types are found among the active and inactive compounds. Possibly studies of spatial dispositions, bond angles, and distances may reveal fruitful correlations.

Since very few drugs act by a single mechanism, the clinical relief which is obtained upon their use is the result of the accumulation of various activities and of attacks upon different cell and enzyme systems. This is probably true with the antihistaminic drugs. Some sort of easily reversible union probably occurs between the competing drug and a receptor in the tissue for which both have an affinity. Such a union might be in the nature of a loose chemical bond or a process of adsorption. Thus, the physicochemical principles governing chemical or adsorptive equilibria may be the keys for the interpretation of this system of

antagonists. Wells (449) has presented fascinating hypothetical kinetic equations for histamine antagonism.

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TABLE 1
Prominent antihistamines

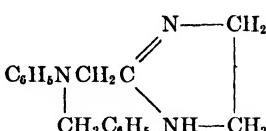
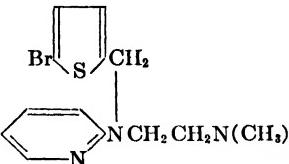
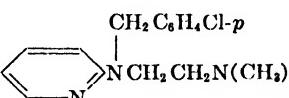
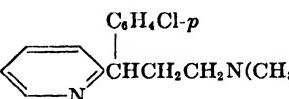
COMMON NAME AND/OR CODE NUMBER	CHEMICAL NAME	FORMULA
1. AH 853, Toladryl, Neobenodine	β -(<i>m</i> -Methyl)benzhydryloxyethylidemethylamine	$m\text{-CH}_3\text{C}_6\text{H}_4\text{CHOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ 
2. Antistine, Antazoline, Phenazoline	2-(<i>N</i> -Benzylanilino-methyl)-2-imidazoline* 2-(<i>N</i> -Benzyl- <i>N</i> -phenylaminomethyl)-imidazoline	 $\text{C}_6\text{H}_5\text{NH}_2\text{CH}_2\text{C}=\text{N}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2$
3. Benadryl, Diphenhydramine, A 424, S 51	2-(Benzhydryloxy)- <i>N,N</i> -dimethylethylamine* β -Dimethylaminoethyl benzhydryl ether	$(\text{C}_6\text{H}_5)_2\text{CHOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$
4. Bristol C-5581-H, Lilly 01500	[2-(<i>o</i> -Benzylphenoxy)-ethyl]dimethylamine* 2-Benzylphenyl- β -dimethylaminoethyl ether	$\text{o-C}_6\text{H}_5\text{CH}_2\text{C}_6\text{H}_4\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$
5. Bromothen	2-[(5-Bromo-2-thenyl)-(2-dimethylaminoethyl)amino]pyridine* <i>N'</i> -2-Pyridyl- <i>N'</i> -5-bromoethyl- <i>N,N</i> -dimethylethylenediamine	 $\text{Br}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2)$
6. Chlorneoantergan	2-[(4-Chlorobenzyl)(2-dimethylaminoethyl)amino]pyridine* <i>N'</i> - <i>p</i> -Chlorobenzyl- <i>N'</i> -2-pyridyl- <i>N,N</i> -dimethylethylenediamine	 $\text{CH}_2\text{C}_6\text{H}_4\text{Cl}-p-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2)$
7. Chlortrimeton, Chlorprophenpyridamine	2-[(4-Chlorophenyl)-(2-dimethylaminoethyl)amino]pyridine* 1-(<i>p</i> -Chlorophenyl)-1-(2-pyridyl)-3- <i>N,N</i> -dimethylpropylamine	 $\text{C}_6\text{H}_4\text{Cl}-p-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2)$

TABLE 1—Continued

COMMON NAME AND/OR CODE NUMBER	CHEMICAL NAME	FORMULA
8. Decapryn, Doxyl-amine	2-[α -(2-Dimethylaminoethoxy)- α -methylbenzyl]pyridine	<p style="text-align: center;"> $\begin{array}{c} \text{CH}_3 \\ \\ \text{C}_6\text{H}_5\text{COCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \\ \\ \text{N} \\ \text{C}_6\text{H}_5 \end{array}$ </p>
9. Diatrin	N,N -Dimethyl- N' -phenyl- N' -2-thenylethylenediamine* N,N -Dimethyl- N' -phenyl- N' -(2-thienylmethyl)ethylenediamine	<p style="text-align: center;"> $\begin{array}{c} \text{S} \\ \\ \text{CH}_2 \\ \\ \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \end{array}$ </p>
10. Dramamine, Dimenhydrinate	β -Dimethylaminoethyl benzhydryl ether 8-chlorotheophyllinate	$(\text{C}_6\text{H}_5)_2\text{CHOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \cdot$ $\begin{array}{c} \text{CH}_3\text{N}-\text{CO} \\ \\ \text{OC} \\ \\ \text{CH}_3\text{N}-\text{C}=\text{C}-\text{NH} \\ \\ \text{CCl} \end{array}$
11. Foralamin, Methafurylene, F 150	N -2-Furylmethyl- N -2-pyridyl- N',N' -dimethylethylenediamine	<p style="text-align: center;"> $\begin{array}{c} \text{O} \\ \\ \text{CH}_2 \\ \\ \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \end{array}$ </p>
12. Hetramine	2-[Benzyl(2-dimethylaminoethyl)amino]-pyrimidine* N' -Benzyl- N' -2-pyrimidyl- N,N -dimethylethylenediamine	<p style="text-align: center;"> $\begin{array}{c} \text{CH}_2\text{C}_6\text{H}_5 \\ \\ \text{N} \\ \text{C}_6\text{H}_5=\text{N} \\ \\ \text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \end{array}$ </p>
13. Linadryl, A 446	β -Morpholinylethyl benzhydryl ether	$(\text{C}_6\text{H}_5)_2\text{CHOCH}_2\text{CH}_2\text{N}$
14. Lilly 01003	1,2-Diphenyl-4-piperidyl-1-butene	$\text{C}_6\text{H}_5\text{CH}=\text{CCH}_2\text{CH}_2\text{N}$

TABLE 1—Continued

COMMON NAME AND/OR CODE NUMBER	CHEMICAL NAME	FORMULA
15. Neoantergan, Mepyramine, Pyranisamine, Anthisan, RP 2786	2-[(2-Dimethylaminoethyl)(p-methoxybenzyl)amino]pyridine* N'-p-Methoxybenzyl-N'-pyridyl-N,N-dimethylethylenediamine	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2$
16. Neohetramine, Thonzylamine, Anahist	2-[(2-Dimethylaminoethyl)(p-methoxybenzyl)amino]pyrimidine* N'-p-Methoxybenzyl-N'-2-pyrimidyl-N,N-dimethylethylenediamine	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2$
17. Perazil, Chlorcyclizine, Diparalene, 47-282, AH 289	N-Methyl-N'-(4-chlorobenzhydryl)piperazine	$\text{C}_6\text{H}_5\text{CHIN}$
18. Phenergan, RP 3277	10-(2-Dimethylaminoisopropyl)phenothiazine* N,N-Dimethylaminoisopropylthiodiphenylamine	
19. Pyribenzamine, Tripeleannamine, C 63	2-[Benzyl(2-dimethylaminoethyl)amino]pyridine* N,N-Dimethyl-N'-benzyl-N'-2-pyridyl-ethylenediamine	
20. Pyrrolazote, Pyrathiazine	10-(2-Pyrrolidylethyl)phenothiazine* (β -Pyrrolidylethyl)phenothiazine	
21. Searle 1675	N-(2-Dimethylaminoethyl)acridine N-(β -Dimethylaminoethyl)acridine	

TABLE 1—*Concluded*

COMMON NAME AND/OR CODE NUMBER	CHEMICAL NAME	FORMULA
22. Tagathen, Chlorothen (cit- rate)	2-[(5-Chloro-2-thenyl)- (2-dimethylamino- ethyl)amino]pyri- dine* (citrate) <i>N'</i> -2-Pyridyl- <i>N</i> '-2- chlorothienyl- <i>N,N</i> - dimethylethylenedi- amine	
23. Thenfadil, WIN 2848	2-[(2-Dimethylamino- ethyl)-3-thenyl- amino]pyridine <i>N,N</i> -Dimethyl- <i>N'</i> -(3- thenyl)- <i>N'</i> -(2-pyri- dyl)ethylenediamine	
24. Thenylene, His- tadyl, Pyrathyn, Methapyrilene, Thenylpyramine, AII 42, Lilly 01013	2-[(2-Dimethylamino- ethyl)-2-thenyl- amino]pyridine <i>N'</i> -2-Pyridyl- <i>N'</i> -2- thenyl- <i>N,N</i> -di- methylethylenedi- amine	
25. Thephorin, Phenindamine, Nu 1504	2-Methyl-9-phenyl- 2,3,4,9-tetrahydro- 1-pyridindene	
26. Trimeton, Pro- phenpyridamine	1-Phenyl-2-(2-pyri- dyl)-3-dimethyl- aminopropane	
27. White 194B	<i>N'</i> -2-Thiazolyl- <i>N</i> '- <i>p</i> - methoxybenzyl- <i>N,N</i> -dimethylethylenedi- amine	

* Name given in *Chemical Abstracts*.

TABLE 2
Color reactions of antihistamines (168, 171, 172, 173, 174, 221)

REAGENT	BENADRYL HYDRO-CHLORIDE	PYRILENZAMINE HYDRO-CHLORIDE	HISTADYL HYDRO-CHLORIDE	BROMOTETEN HYDRO-CHLORIDE	CHLOROTHEN HYDRO-CHLORIDE	TAGATHEN (CHLOROTHEN CITRATE)
H ₂ SO ₄ (conc.)	Orange	Greenish yellow	Burnt orange, changing to blood-red; finally deep purple	Magenta; then deep purple	Magenta, then deep purple	Magenta; then deep purple
HNO ₃ (conc.)	No reaction	No reaction	Purple-pink, changing to brown	Orange, changing to lemon-yellow	Yellow	Orange-red
Mandelin's	Red with oily red globules	Chocolate-brown	Burnt orange	Deep reddish orange	Deep reddish orange	Deep reddish orange
Marquis'	Canary-yellow, reddish orange, then chocolate-brown	Red, then deep reddish brown	Orange-brown, changing to purplish pink	Bright red	Carmine red with a slight purple cast	Brilliant magenta
Frohde's	Canary-yellow, then orange-red	Pale pink, then rust-red	Dark brown with black streaks	Deep reddish purple	Deep reddish purple	Deep reddish purple
Chloroplatinic acid	Granular orange precipitate; leaf-like crystals in crosses; cigar shape for some of the crystals	Granular orange precipitate; rosettes and sheaves of flat plates on drying	Branched bundles of rods in feather-like agglomerates	Amorphous precipitate	Amorphous precipitate	Amorphous precipitate
Chloroauric acid	Granular yellow precipitate	Granular yellow precipitate	Amorphous precipitate	Amorphous precipitate	Amorphous precipitate	Amorphous precipitate
Pieric acid (saturated aqueous solution)	Granular yellow precipitate	Granular yellow precipitate	Amorphous precipitate	Amorphous precipitate	Amorphous precipitate	Amorphous precipitate
Buckingham's			Brown; then black	Deep reddish purple	Deep reddish purple	Deep reddish purple

TABLE 2—Continued

REAGENT	TRIMPTON	THEPHORIN	SC 887 ^(a)	F 929	F 1571	DIATRIN
H ₂ SO ₄ , (conc.)	Colorless	Canary-yellow	Deep orange-yellow	Yellow then pink	Orange	Orange-yellow
HNO ₃ , (conc.)	Canary-yellow	Colorless	Very faint yellow	Deep blue	Lemon-yellow; then orange	Brownish red
Mandelin's	Colorless	Greenish blue; then deep blue	Faint greenish yellow	Pale brown with purple center	Bright orange	Orange-red, changing to pale yellow
Marquis'	Colorless	Pale brown	Carmine	Pale yellow	Pale yellow	
Frohde's	Colorless	Greenish yellow	Pale green; then red-violet	Colorless	Orange	
Chloroplatinic acid	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous
Chloroauric acid	Amorphous	Amorphous	Amorphous	Square flat plates of varying sizes	Amorphous	Amorphous
Picric acid (saturated aqueous solution)	Thin small needles in crosses and bundles	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous
Buckingham's	Colorless	Olive-green	Green to bluish green	Bluish green; then red-brown to black	Colorless	Orange-red

(a) Diethylaminoethyl 9,10-dihydroanthracene-10-carboxylate.

REAGENT	DRAAMINE	NEOHETRAMINE	NEOANTERGAN	LINDAEXYL HYDROCHLORIDE A 446		ANTISTINE	NO. 204 (b)
				DECAPRYN	LINDAEXYL HYDROCHLORIDE A 446		
H ₂ SO ₄ (concd.)	No change	Red	Magenta	Canary-yellow	Canary-yellow with oily orange-red droplets	Colorless	Bright orange
HNO ₃ (concd.)	No change	Colorless	Colorless	Colorless	Colorless	Magenta ^a	Colorless
Mandelin's	Cloudy bluish	Deep pink	Magenta	No change	No change	Brick-red	No change
Marquis'	Cloudy tan	Magenta	Magenta	No change	No change	No change	Pale yellow
Frohde's	No change	Magenta	Magenta	Canary-yellow; then orange	Canary-yellow with oily orange-red droplets	Colorless	Canary-yellow with oily orange droplets
Chloroplatinic acid	Amorphous	Amorphous	Amorphous	Amorphous; then oily glob- ules	Leaf-like agglomerates in bundles	Amorphous	Amorphous
Chloroauric acid	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous
Picric acid (saturated aqueous solu- tion)	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous
Buckingham's	No change	Magenta	Magenta	Canary-yellow; then dirty green	Canary-yellow with oily orange-red droplets	Colorless	Canary-yellow with oily orange drops

^a 2-Imidazolyl-1-methyl benzhydryl ether.

TABLE 2—*Concluded*

REAGENT	SC 1627, RP 3015 ^(e)	SC 1742 ^(d)	SC 1898 ^(e)	SC 1923 ^(f)	PHENEGAN, RP 3277	PYROLAZOTE
H ₂ SO ₄ (conc.)	Pink	Pink	Magenta	Fucia	Magenta	Magenta
HNO ₃ (conc.)	Magenta, changing immediately to orange-yellow	Brilliant red, changing immediately to orange-yellow	Magenta, changing immediately to orange-yellow	Magenta, changing immediately to orange-yellow	Magenta, changing immediately to greenish yellow	Magenta, changing immediately to greenish yellow
Mandelin's	Pink	Pink	Pink	Pink	Pink	Pink
Marquis'	Magenta	Magenta	Magenta	Magenta	Magenta	Magenta
Frohde's	Pink	Pink	Pink	Pink	Pink	Pink
Chloroplatinic acid	Black amorphous mass; reagent turns blue-green	Black amorphous mass; reagent turns blue-green	Black amorphous mass; reagent turns blue-green	Black amorphous mass; reagent turns blue-green	Flat purple leaf-like crystals, single or in crosses; reagent turns blue-green	Purple, pointed rods; reagent turns blue-green
Chloroauric acid	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous
Picric acid (saturated aqueous solution)	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous
Buckingham's	Deep red	Chocolate-brown	Reddish brown	Brownish black	Brilliant red, changing to magenta	Magenta; then brown; finally black

^(e) N-Dimethylaminoethoxythiodiphenylamine hydrochloride.^(d) N-Trimethylaminoethylthiodiphenylamine chloride.^(f) N-Dimethylethanolaminoethylthiodiphenylamine bromide.

(f) N-Methylethanolaminoethylthiodiphenylamine hydrochloride.

TABLE 3
Phenolic ethers

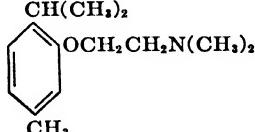
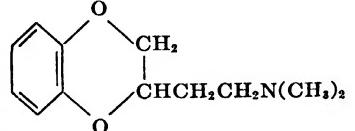
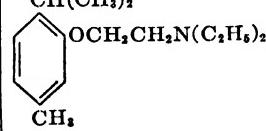
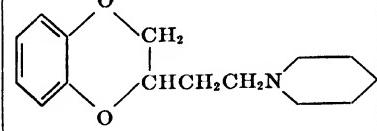
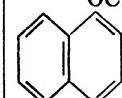
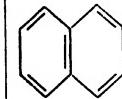
FOURNEAU CODE NO.	STRUCTURE	A.H. INDEX*	TOXICITY FOR RABBITS		REMARKS	REFERENCES
			M.T.D.† g./kg.	M.L.D.‡ g./kg.		
Tostra- mine...	 CH(CH ₃) ₂ OCH ₂ CH ₂ N(CH ₃) ₂ CH ₃	4			Better tolerated by humans than F 929	(7, 8)
F 883, Prosym- pal...		1			Less active and less toxic than F 929	(33, 36, 37, 38, 140, 141, 145, 439)
F 928...	C ₆ H ₅ OCH ₂ CH ₂ N(C ₂ H ₅) ₂	1	0.015	0.055	Less active than F 929	(38, 407)
F 929...	 CH(CH ₃) ₂ OCH ₂ CH ₂ N(C ₂ H ₅) ₂ CH ₃	3	0.005	0.025	Most active ether	(cf. 235)
F 933...					Solution of 1:10 ⁵ inhibited 1 γ/10 ml. histamine	(38, 433, 434)
F 936...	p-CH ₃ C ₆ H ₄ OCH ₂ CH ₂ N(C ₂ H ₅) ₂	1	0.010	0.040	Inactive	(407)
F 937...					Almost inactive; delayed but did not prevent death	(38)
F 939...					Less active than F 929; 30-60 per cent of animals saved from death	(38)

TABLE 3—Continued

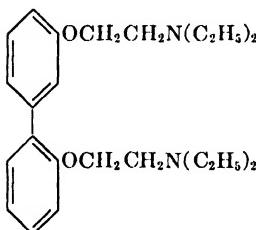
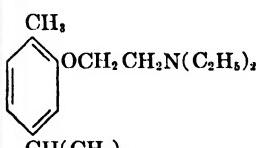
FOURNEAU CODE NO.	STRUCTURE	A.H. IN- DEX*	TOXICITY FOR RABBITS		REMARKS	REFERENCES
			M.T.D. †	M.L.D. ‡		
F 940...	<i>p</i> -CH ₃ OC ₆ H ₄ OCH ₂ CH ₂ N(C ₂ H ₅) ₂				Less active than F 929; 30-60 per cent of animals saved from death	(38)
F 1262...	<i>o</i> -C ₆ H ₅ C ₆ H ₄ OCH ₂ CH ₂ N(C ₂ H ₅) ₂				Prevents anaphylactic shock in rabbits; nontoxic	(407, 439)
F 1271...	 <chem>*c1ccc(OCCN(CC)N(CC)C)c(*)cc1</chem>				Less active than F 929; 30-60 per cent of animals saved from death	(38)
F 1274...	<i>p</i> -CH ₂ =CHCH ₂ C ₆ H ₄ O-CH ₂ CH ₂ N(C ₂ H ₅) ₂				Inactive	(407)
F 1306...	<i>p</i> -C ₆ H ₅ C ₆ H ₄ OCH ₂ CH ₂ N(C ₂ H ₅) ₂				Almost inactive; 30-60 per cent of animals saved from death	(38, 407)
F 1323...	<i>m</i> -C ₆ H ₅ C ₆ H ₄ OCH ₂ CH ₂ N(C ₂ H ₅) ₂				Inactive	(407)
F 1379...	 <chem>*c1ccc(OCCN(CC)N(CC)C)cc1CC(C)C</chem>	3	0.005	0.025	Same activity as F 929	(407)

TABLE 3—Continued

FOURNEAU CODE NO.	STRUCTURE	A.H. IN- DEX*	TOXICITY FOR RABBITS		REMARKS	REFERENCES
			M.T.D. [†] g./kg.	M.L.D. [‡] g./kg.		
F 1464..		2	0.010	0.030	Less active than F 929	(407)
F 1465..		2			Same activity as F 1464	(407)
F 1482..		1	0.010	0.035	Inactive	(407)
F 1483..					Inactive	(407)
F 1655..		2	0.010	0.020	Less active than F 929	(407)
F 1702..	<i>o</i> -CH ₃ C ₆ H ₄ OCH ₂ CH ₂ N(C ₂ H ₅) ₂	1			Inactive	(407)
F 1703..	<i>m</i> -CH ₃ C ₆ H ₄ OCH ₂ CH ₂ N(C ₂ H ₅) ₂				Inactive	(407)
					Inactive	(407)
					Augmented the action of histamine	(26)

TABLE 3—Concluded

TOURNEAU CODE NO.	STRUCTURE	A.H. IN- DEX*	TOXICITY FOR RABBITS		REMARKS	REFERENCES
			† M.T.D. g./kg.	‡ MLD. g./kg.		
	<i>m</i> -HOC ₆ H ₄ OCH ₂ CH ₂ NHCH ₃				Augmented the vaso- dilating action of histamine	(19)
	<i>p</i> -HOC ₆ H ₄ OCH ₂ CH ₂ NHCH ₃				Augmented the vaso- dilating action of histamine	(19)
	<i>p</i> -C ₆ H ₅ C ₆ H ₄ OCH ₂ CH ₂ NH ₂				Augmented the action of hista- mine	(26)
	C ₆ H ₅ OCH ₂ CHOCH ₂ CH ₂ NH ₂				Augmented the action of hista- mine	(26)
	<i>o</i> -CH ₃ OC ₆ H ₄ O- CH ₂ CH ₂ OCH ₂ CH ₂ NH ₂				Augmented the action of hista- mine	(26)
	C ₆ H ₅ OCH ₂ CH ₂ N(CH ₃) ₂				Augmented the action of hista- mine	(26)
	C ₆ H ₅ OCH ₂ CH ₂ N(C ₂ H ₅) ₂				Augmented the action of hista- mine	(26)
	C ₆ H ₅ OCH ₂ CH ₂ N(CH ₃) ₂				Ineffective; activity resembled that of nicotine	(26)

* Antihistamine index for histamine shock.

† Maximum tolerated dose.

‡ Minimum lethal dose.

TABLE 4
Ethers

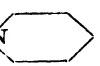
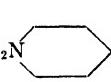
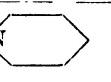
NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	ANTI-HISTAMINE ACTIVITY*	TOXICITY†
Basic aryl ethers (327)					
1 . .	 OCH ₂ CH ₂ N(C ₂ H ₅) ₂  OCH ₂ CH ₂ N(C ₂ H ₅) ₂	°C. 165-175/1-3 mm.	°C. 145 (2HCl)	mg. 2-4	mg./kg.
2 . .	 OCH ₂ CH ₂ N(C ₂ H ₅) ₂ OCH ₂ CH ₂ N(C ₂ H ₅) ₂	194-200/5 mm.	133 (2HCl) 117-118 (dipicrate)	20	
3 . .	 OCH ₂ CH ₂ N(C ₂ H ₅) ₂ OCH ₂ CH ₂ N(C ₂ H ₅) ₂	178-182/102 mm.	155 (2HCl) 184 (dipicrate)	60	
4 . .	OCH ₂ CH ₂ N(C ₂ H ₅) ₂  OCH ₂ CH ₂ N(C ₂ H ₅) ₂  OCH ₂ CH ₂ N(C ₂ H ₅) ₂		197 (3HCl) 156-157 (tripicrate)	10	
5 . .	OCH ₂ CH ₂ N(C ₂ H ₅) ₂  OCH ₂ CH ₂ N(C ₂ H ₅) ₂ OCH ₂ CH ₂ N(C ₂ H ₅) ₂		161-162 (tripicrate)	55	
6 . .	C ₆ H ₅ CH ₂ OCH ₂ CH ₂ N(C ₂ H ₅) ₂	134-136/1 mm.	63-64 (picrate)	16.5	
7 . .	C ₆ H ₅ CH ₂ OCH ₂ CH ₂ N 	184-185/1 mm. 167-168/ 0.4-0.5 mm.	169 (HCl) 144.5 (HBr) 188 (CH ₃ I) 123-125 (C ₂ H ₅ Br)	0.210	100
8 . .	(C ₆ H ₅) ₂ CHOCH ₂ CH ₂ N(C ₂ H ₅) ₂		144 (HCl)	0.06	87.5

TABLE 4—Concluded

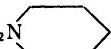
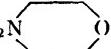
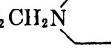
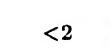
NO.	FORMULA	BOILING POINT °C. mm.	MELTING POINT OF SALT °C.	ANTI- HISTA- MINE ACTIV- ITY*	TOXIC- ITY† mg./kg.
Basic aryl ethers (327)					
9 . .	(C ₆ H ₅) ₃ COCH ₂ CH ₂ N(C ₂ H ₅) ₂	200–206/1 mm.	158–160 (HCl)	1	
10 . .	C ₆ H ₅ CH ₂ CHOCH ₂ CH ₂ N(CH ₃) ₂ C ₆ H ₅	169–171/2–3 mm.	116–117 (HCl)	1	
11 . .	C ₆ H ₅ CH ₂ CHOCH ₂ CH ₂ N C ₆ H ₅ 	190–195/3 mm.	123–124 (hy- drochloride)	0.220	86
Thioethers (327)					
12 . .	(C ₆ H ₅) ₂ CHSCH ₂ CH ₂ N 		176–177 (hy- drochloride)	1	
13 . .	(C ₆ H ₅) ₂ CHSCH ₂ CH ₂ N(C ₂ H ₅) ₂		100–105 (hy- drochloride)	0.5	242
Thioethers (31)					
14 . .	C ₆ H ₅ SCH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂	190–193/12 mm.	83–84 (hydro- chloride)		
15 . .	C ₆ H ₅ SCH ₂ CHOHCH ₂ N(C ₂ H ₅) ₂	168–171/4 mm.			
16 . .	<i>o</i> -CH ₃ C ₆ H ₄ SCH ₂ CH ₂ N(C ₂ H ₅) ₂	150–153/5 mm.	126–127 (hy- drochloride)		
17 . .	<i>o</i> -CH ₃ C ₆ H ₄ SCH ₂ CHOHCH ₂ N(C ₂ H ₅) ₂	153–157/1 mm.			
18 . .	<i>m</i> -CH ₃ C ₆ H ₄ SCH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂	168–173/13 mm.	65–66 (hydro- chloride)		
19 . .	<i>m</i> -CH ₃ C ₆ H ₄ SCH ₂ CHOHCH ₂ N(C ₂ H ₅) ₂	168–172/3 mm.			
20 . .	<i>p</i> -CH ₃ C ₆ H ₄ SCH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂	155–158/7 mm.	97–98 (hydro- chloride)		
21 . .	<i>p</i> -CH ₃ C ₆ H ₄ SCH ₂ CHOHCH ₂ N(C ₂ H ₅) ₂	168–172/3 mm.			

* Milligrams necessary to neutralize contraction of isolated guinea-pig intestine caused by 0.01 mg. histamine.

† Milligrams per kilogram necessary to kill 50 per cent of the test animals.

TABLE 5

Efficacy of benzhydryl alkamine ethers in preventing fatal histamine-induced bronchoconstriction in guinea pigs (263)
 $(C_6H_5)_2CHOR$

NO.	R	ANTIHISTAMINE ACTIVITY INDEX*	L.D. ₅₀ †
1 . . .	$-CH_2CH_2N(CH_3)_2$	33	82
2 . . .	$-CH_2CH_2N$ 	33	80
3 . . .	$-CH_2CH_2N$ 	16	185
4 . . .	$-CH_2CH_2NHCH_3$	8	85
5 . . .	$-CH_2CH_2NHCH(CH_3)_2$	8	72
6 . . .	$-CH_2CH_2CH_2N(C_2H_5)_2$	8	85
7 . . .	$-CH_2CH_2N(C_2H_5)_2$	4	55
8 . . .	$-CH_2CH_2CH_2N$ 	4	
9 . . .	$-CH_2CH_2NHH_2$	2	50
10 . . .	$-CH_2CH_2NHCH_2CH_2N$ 	2	92
11 . . .	$(p-ClC_6H_4)_2CHOCH_2CH_2N$  O‡	2	390
12 . . .	$-CH_2CH_2CH_2CH_2CH_2CH_2CH_2N$ 	1	254
13 . . .	$-CH_2CH_2NHCH_2CH_2CH_2CH_3$	<4	50
14 . . .	$-CH_2C(CH_3)_2N$ 	<2	
15 . . .	$-CH_2CH_2OCH_2CH_2N(C_2H_5)_2$	<1	71
16 . . .	$-CH_2CH_2N$ (cyclo-C ₆ H ₁₁) ₂		Very weak
17 . . .	$-CH_2CH_2N(n-C_4H_9)_2$		

* Efficacy in the prevention of fatal histamine-induced bronchoconstriction in guinea pigs. Aminophylline = 1.

† Dose administered intraperitoneally to kill 50 per cent of test animals.

‡ Formula of compound.

TABLE 6
Benzhydryl ethers and thioethers

NO.	R	(C ₆ H ₅) ₂ CHOR	BOILING POINT mm.	MELTING POINT OF SALT (OR BASE)	REFERENCES
1.....	-CH ₂ CH ₂ NH ₂		150-158/0.3	74 °C.	(263, 415)
2.....	-CH ₂ CH ₂ NHCH ₃			159 (HCl)	(349)
3.....	-CH ₂ CH ₂ NHC ₄ H ₉			100 (base)	(263)
4.....	-CH ₂ CH ₂ NHC ₆ H ₅			210 (HCl)	(98)
5.....	-CH ₂ CH ₂ NHCH ₂ C ₆ H ₅		182-184/0.4-0.6	182 (HBr)	(415)
6.....	-CH ₂ CH ₂ N(CH ₃) ₂		150-165/2 mm.	167 (HCl)	(299, 349, 354, 356, 459)
7.....	-CH ₂ CH ₂ N(C ₂ H ₅) ₂		190-202/11 mm. 155-158/1.5 mm.	146 (HCl)	(6, 299, 327, 331, 349, 354)
8.....	-CH(CH ₃)CH ₂ N(CH ₃) ₂		122/0.5 mm. 138-140/1.5 mm.	150 (HCl) 162 (oxalate)	(6, 331, 356, 358)
9.....	-CH ₂ CH ₂ NHCH(CH ₃) ₂		138-140/1.5 mm.	169 (HCl)	(127, 349)
10.....	-C(CH ₃) ₂ CH ₂ N(C ₂ H ₅) ₂				(358)
11.....	-CH(C ₂ H ₅)CH ₂ N(CH ₃) ₂				(358)
12.....	-CH ₂ C(CH ₃) ₂ N(CH ₃) ₂				(6, 331)
13.....	-CH ₂ CH(CH ₃)N(CH ₃) ₂				(6, 331)

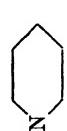
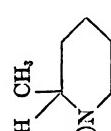
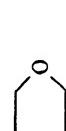
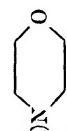
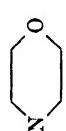
14.....	$-\text{C}(\text{CH}_3)_2\text{CH}_2\text{N}(\text{CH}_3)_2$	140-143/2 mm. 148/2 mm.	200 (HCl) 98 (acid succinate)	(6, 331) (6, 299, 331, 355)
15.....	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$			
16.....	$-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$			
17.....	$-\text{CH}_2\text{C}(\text{CH}_3)\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	182-183/4.5 mm.		(355)
18.....	$-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$			
19.....	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$			
20.....	$-\text{CH}_2\text{CH}_2\text{N}$ 	161-165/0.7 mm.	132 (HCl) 165 (CH ₃ I)	(356, 463)
21.....	$-\text{CH}_2\text{CH}_2\text{N}$ 	205/6 mm.	169 (HCl)	(80, 299, 349, 356, 413)
22.....	$-\text{CH}_2\text{CH}(\text{CH}_3)\text{N}$ 			(357)
23.....	$\begin{array}{c} \text{H} \\ \\ \text{CH}_2\text{CH}(\text{CH}_3)\text{N} \end{array}$ 			
24.....	$-\text{CH}_2\text{CH}_2\text{N}$ 		183 (HCl)	(170, 260, 263, 299, 349, 356)
25.....	$-\text{CH}_2\text{CH}(\text{CH}_3)\text{N}$ 			(357)
26.....	$-\text{CH}_2\text{CH}_2\text{N}$ 			(356)
27.....	$-\text{CH}_2\text{C}(\text{CH}_3)_2\text{N}$ 			(263)

TABLE 6—Continued

NO.	R	BOILING POINT °C.	MELTING POINT OF SALT (OR BASE)	REFERENCES
28.....	$-\text{CH}_2\text{C}(\text{CH}_3)_2\text{N}$ 			(357)
29.....	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ 			(357)
30.....	$-\text{CH}_2\text{CH}_2\text{N}$ 		53 190 (2HCl)	(463) (263, 356)
31.....	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_6\text{H}_5)_2$			
32.....	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ 			(356)
33.....	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ 			(356)
34.....	NCH_3 			206 (HCl)
35.....	NCH_2CH_3 			(226)
36.....	NC_2H_5 			(226)

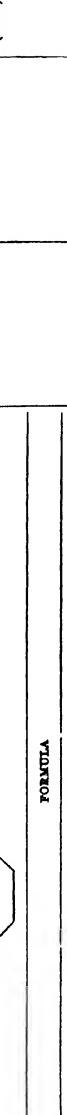
 37	 38	 39	 40	 41	 42	 43	<hr style="border-top: 1px solid black; margin-bottom: 5px;"/> <div style="text-align: center;">FORMULA</div> <hr style="border-top: 1px solid black; margin-top: 5px;"/> <div style="text-align: center;"> $m\text{-CH}_2\text{C}_6\text{H}_4\text{CHOC}_2\text{H}_5\text{CH}_2\text{N}(\text{CH}_3)_2$ </div> 44	 45	 46	 47
(226)	(263)	(357)	(263, 357)	(6, 331)	(6, 331)	(357)	(279, 385)	(349)	(349)	(358)

TABLE 6—Continued

NO.	FORMULA	BOILING POINT °C.	MELTING POINT OF SALT (OR BASE) °C.	REFERENCES
48.....	$(\text{CH}_3)_2\text{CCH}_2\text{C}(\text{CH}_3)_2$			(127)
49.....	$(p\text{-CH}_3\text{C}_6\text{H}_4)\text{CHOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$			(299, 349)
50.....	$o\text{-CH}_3\text{C}_6\text{H}_4\text{CHOCH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}$			(357)
51.....	$o\text{-CH}_3\text{C}_6\text{H}_4\text{CHOCH}_2\text{CH}_2\text{N}$		75-83/7 mm.	(326)
52.....	$m\text{-CH}_3\text{C}_6\text{H}_4\text{CHOCH}_2\text{CH}_2\text{N}$		196-200/1.3 mm.	(326)
53.....	$p\text{-CH}_3\text{C}_6\text{H}_4\text{CHOCH}_2\text{CH}_2\text{N}$		190-192	(326)
54.....	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CHOCH}_2\text{CH}_2\text{NHCCH}(\text{CH}_3)_2$			(4)
55.....	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CHOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$		137-139/0.1 mm.	(159)

56.....	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CHOCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	(4)
57.....	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CHOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	(4)
58.....	$m\text{-C}_6\text{H}_5\text{OC}_6\text{H}_4\text{CHOCH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	(357)
59.....	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CHOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	(463)
60.....	$(o\text{-CH}_3\text{OC}_6\text{H}_4)_2\text{CHOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	218-220/0.35 nm.
61.....	$(o\text{-CH}_3\text{OC}_6\text{H}_4)_2\text{CHOCH}(\text{CH}_3)\text{CH}_2\text{N}(\text{CH}_3)_2$	(299)
62.....	$(p\text{-CH}_3\text{OC}_6\text{H}_4)_2\text{CHOCH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	(358)
63.....	$m\text{-ClC}_6\text{H}_4\text{CHOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	(357)
64.....	$m\text{-ClC}_6\text{H}_4\text{CHOCH}_2\text{CH}(\text{CH}_3)\text{N}(\text{C}_2\text{H}_5)_2$	(290)
		(358)

TABLE 6—Continued

NO.	FORMULA	BOILING POINT °C.	MELTING POINT OF SALT (OR BASE) °C.	REFERENCES
65.....	$m\text{-ClC}_6\text{H}_4\text{CHOCH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{N}(i\text{-C}_3\text{H}_7)_2$ 		(358)	
66.....	$\text{o-CH}_3\text{C}_6\text{H}_4\text{CHOCH}_2\text{C}(\text{CH}_3)_2\text{N}(\text{C}_2\text{H}_5)_2\text{O}$ 		(357)	
67.....	$(p\text{-ClC}_6\text{H}_4)_2\text{COCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2\text{O}$ 		(263)	
68.....	$(p\text{-ClC}_6\text{H}_4)_2\text{COCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2\text{S}$ 		(357)	
69.....	$(\text{C}_6\text{H}_5)_2\text{C}(\text{CH}_3)\text{OCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ 	198-199/13 mm.	(69)	
70.....	$(\text{C}_6\text{H}_5)_2\text{C}(\text{CH}_3)\text{OCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ 	222/13 mm.	(69)	
71.....	$(\text{C}_6\text{H}_5)_2\text{C}(\text{C}_2\text{H}_5)_2\text{OCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ 	236/14 mm.	(69)	
72.....	$(\text{C}_6\text{H}_5)_2\text{C}(\text{C}_2\text{H}_5)_2\text{OCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ 	231/760 mm.	(69)	
73.....	$(\text{C}_6\text{H}_5)_2\text{COCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ 		(6)	
74.....	$(\text{C}_6\text{H}_5)_2\text{COCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ 	248-250/14 mm.	(69, 327)	
75.....	$(\text{C}_6\text{H}_5)_2\text{COCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ 	140 (HCl)	(69)	97

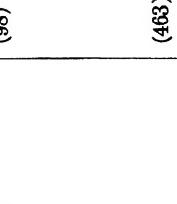
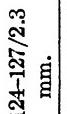
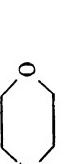
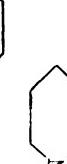
76.....	$(C_6H_5)_2CH SCH_2 CH_2 N(C_2H_5)_2$	175-178/1-2 mm.	100-105 (HCl)	(65, 327)
	R			
77.....	$-CH_2 CH_2 NCH(C_6H_5)_2$ 	109		(98)
	CH ₂ C ₆ H ₅			
78.....	formula $(n-C_4H_9)_2CHOCH_2CH_2N$ 	124-127/2.3 mm.	(463)	
		(C ₆ H ₅) ₂ CHSR (360)		
79.....	$-CH_2 CH_2 N(CH_3)_2$		183 (HCl)	(360)
	$-CH_2 CH_2 N$ 		180 (HCl)	(360)
80.....	$-CH_2 CH_2 N$ 			(360)
81.....	$-CH_2 CH_2 CH_2 N(CH_3)_2$			(360)
82.....	$-CH_2 CH_2 CH_2 N(C_4H_9)_2$			(360)
83.....	$-CH(C_6H_5)CH_2 N(CH_3)_2$			(360)
84.....	$-CH_2 CH_2 CH_2 CH_2 CH_2 N$ 			(360)
85.....	$-CH_2 C(CH_3)_2 CH_2 N$ 			(360)
86.....	$-CH_2 CH_2 NHCH_3$			(360)

TABLE 6—Concluded

NO.	R	BOILING POINT °C.	MELTING POINT OF SALT (OR BASE) °C.	REFERENCES
87.....	—CH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂			(360)
88.....			177 (HCl)	(327)
89.....	FORMULA			(360)
90.....	(p-CH ₃ C ₆ H ₄) ₂ CHSCH ₂ CH ₂ N(C ₂ H ₅) ₂			(360)
91.....				(92)

TABLE 6A
Activity of salts of benzhydryl ethers studied by Alles and Redemann (6)

NO.*	ANTIHISTAMINE ACTIVITY†‡	NO.*	ANTIHISTAMINE ACTIVITY†‡
	<i>per cent</i>		<i>per cent</i>
6 (Benadryl).....	53-88	13.....	11
7.....	33	14.....	46
8.....	20	15.....	61 (acid succinate)
12.....	3	73.....	10

* The numbers correspond to those in table 6.

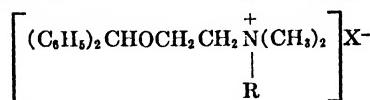
† Average reduction of response of guinea-pig ileum to 5×10^{-7} molal histamine.

‡ Hydrochloride unless otherwise stated.

TABLE 7
Haloxanthine salts of benzhydryl ethers (101)
 $(C_6H_5)_2CHO(CH_2)_nR$

NO.	n	R	SALT	MELTING POINT °C.
1.....	2	$-N(CH_2)_2$	8-Chlorotheophyllinate	104
2.....	2	$-N(CH_2)_2$	8-Bromotheophyllinate	113
3.....	2	$-N(CH_2)_2$	8-Iodotheophyllinate	
4.....	2	$-N(C_2H_5)_2$	8-Chlorotheophyllinate	
5.....	3	$-N(CH_2)_2$	8-Bromotheophyllinate	
6.....	2	$-N(CH_2)C_2H_4OH$	8-Chlorotheophyllinate	225-230
BASE				
7.....	$(p-IC_6H_4)_2CHOCH_2CH_2N(CH_3)_2$		8-Chlorotheophyllinate	

TABLE 8
Quaternary ammonium salts of benzhydryl ethers



NO.	R	X	MELTING POINT °C.	REFERENCES
1.....	CH ₃	Cl	177	(262, 350, 459)
2.....	CH ₃	Br	194	(211, 350, 459)
3.....	CH ₃	I	193	(211, 262, 350, 459)
4.....	CH ₃	CH ₃ SO ₄	153	(352, 459)
5.....	CH ₃	p-Toluenesulfonate	153	(127, 352, 459)
6.....	C ₂ H ₅	Br	135	(350, 459)
7.....	C ₂ H ₅	Benzenesulfonate	120	(352, 459)
8.....	C ₂ H ₅	I	138	(350)
9.....	C ₂ H ₅	p-Toluenesulfonate	114	(127, 352)
10.....	C ₃ H ₇	p-Toluenesulfonate	133	(352)
11.....	C ₄ H ₉	p-Toluenesulfonate	121	(352)



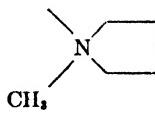
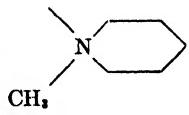
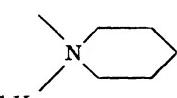
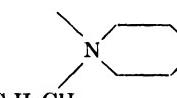
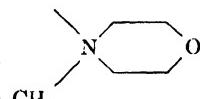
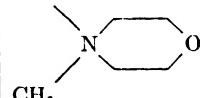
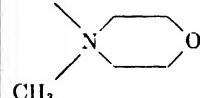
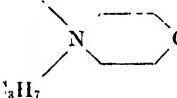
NO.	R ⁺	X	MELTING POINT °C.	REFERENCES
12.....	—N(C ₂ H ₅) ₃	Br	147	(350)
13.....	—N(C ₂ H ₅) ₂ C ₄ H ₉	Br		(350)
14.....	—N(n-C ₈ H ₁₇) ₂ C ₈ H ₇ (i)	Br		(350)
15.....	[—N(CH ₃) ₃] ₂	SO ₄		(262)
16.....	C ₈ H ₁₇	Br	102	(365)
17.....	C ₉ H ₁₉	Br	102	(365)
18.....	C ₁₀ H ₂₁	Br	97	(365)
19.....	C ₁₁ H ₂₃	Br		(365)
20.....		I	165	(463)
21.....		I	182	(350)

TABLE 8—Continued

NO.	R ⁺	X	MELTING POINT	REFERENCES
22.....	 C ₈ H ₇	I	°C.	(350)
23.	 C ₆ H ₅ CH ₂	Cl		(357)
24.....	 CH ₃	I	206	(350)
25.....	 CH ₃	Br	188	(350)
26.	 CH ₃	p-Toluene-sulfonate	138	(127, 352)
27.....	 C ₈ H ₇	I		(350)



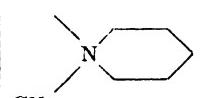
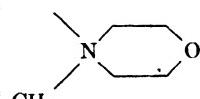
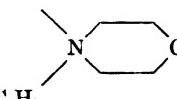
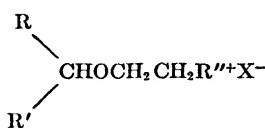
NO.	R ⁺	X	MELTING POINT	REFERENCES
28. .	 CH ₃	Br	°C.	(357)
29.	 CH ₃	I		(350)
30.....	 C ₈ H ₇	I	205	(350)

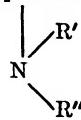
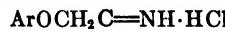
TABLE 8—Concluded



NO.	R	R'	R'' ⁺	X	MELTING POINT °C.	REFER- ENCES
31....	<i>p</i> -CH ₃ OC ₆ H ₄ —	C ₆ H ₅ —	—N(CH ₃) ₃	I	144	(211)
32....	<i>o</i> -CH ₃ OC ₆ H ₄ —	C ₆ H ₅ —	$ \begin{array}{c} \text{CH}_2 \\ \\ \text{—N} \\ \\ \text{C}_2\text{H}_5 \\ \\ \text{CH}_2\text{C}_6\text{H}_5 \end{array} $	Cl		(350)
33....	<i>p</i> -CH ₃ OC ₆ H ₄ —	C ₆ H ₅ —	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{—N} \\ \\ \text{C}_2\text{H}_5 \\ \\ \text{CH}_2\text{C}_6\text{H}_5 \end{array} $	Cl		(350)
34....	<i>p</i> -CH ₃ C ₆ H ₄ —	<i>p</i> -CH ₃ C ₆ H ₄ —	$ \begin{array}{c} \text{—N}(n\text{-C}_3\text{H}_7)_2 \\ \\ \text{C}_3\text{H}_7(i) \end{array} $	Br		(350)

NO.	FORMULA	REFER- ENCE
35....	$ \left[(\text{C}_6\text{H}_5)_2\text{CHOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}^+ \begin{array}{c} + \\ \text{CH}_3 \\ \\ \text{CH}_3 \end{array} \text{O} \right] \text{CH}_3\text{SO}_4^- $	(357)

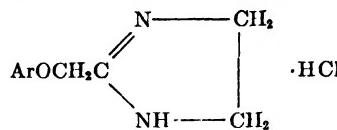
TABLE 9
Aryloxyacetamidine hydrochlorides (113)



NO.	ArO	R'	R''	MELTING POINT °C.	YIELD per cent	ANTIHI-
						TAMINE ACTIVITY*
1...	Phenoxy	H	H	127.5-128.5	72	10
2...	Phenoxy	CH ₃	CH ₃	187-189	77	0
3...	<i>o</i> -Toloxyl	H	H	147.5-148.5	86	0
4...	<i>o</i> -Toloxyl	CH ₃	CH ₃	177-179	88	0
5...	<i>m</i> -Toloxyl	H	H	179-180.5	78	10
6...	<i>m</i> -Toloxyl	CH ₃	CH ₃	200-202	65	0
7...	<i>p</i> -Toloxyl	H	H	169.5-170.5	73	0
8...	<i>p</i> -Toloxyl	CH ₃	CH ₃	173-174.5	75	0
9...	Thymyloxy	H	H	185-185.5	85	1-10
10...	Thymyloxy	CH ₃	CH ₃	197-198	80	10
11...	Thymyloxy	C ₂ H ₅	C ₂ H ₅	212-212.5	57	0.5-1
12...	Thymyloxy	n-C ₃ H ₇	n-C ₃ H ₇	180-182	50	1-10
13...	Thymyloxy	n-C ₄ H ₉	n-C ₄ H ₉	154-155	61	1
14...	Thymyloxy	CH ₃ CH ₂ C ₆ H ₅	H	145-147	71	1-10
15...	Carvaacryloxy	H	H	183.5-184.5	76	10
16...	Carvaacryloxy	CH ₃	CH ₃	178-180	67	1-10
17...	Carvaacryloxy	CH ₃ CH ₂ C ₆ H ₅	H	158.5-159.5	65	0.1-1
18...	3-Methyl-4-chlorophenoxy	H	H	193-194	87	1
19...	3-Methyl-4-chlorophenoxy	CH ₃	CH ₃	183.5-185.5	78	10
20...	<i>o</i> -Isopropylphenoxy	H	H	147.5-149	83	10
21...	<i>o</i> -Isopropylphenoxy	CH ₃	CH ₃	198-198.5	70	10
22...	2,5-Dimethylphenoxy	H	H	215-217	88	0
23...	2,5-Dimethylphenoxy	CH ₃	CH ₃	212-214	87	0

* γ of compound per milliliter of bath liquid, capable of neutralizing the contraction of an isolated guinea-pig gut caused by 1 γ/ml. of histamine diphosphate.

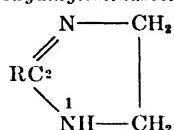
TABLE 10
2-(Aryloxymethyl)imidazoline hydrochlorides (113)



NO.	ArO	MELTING POINT °C.	YIELD <i>per cent</i>	ANTIHISTAMINE ACTIVITY*
				*
24.	Phenoxy	168-169.5	82	10
25.	<i>o</i> -Toloxyl	200-202	71	0
26.	<i>m</i> -Toloxyl	225-227	55	0
27.	<i>p</i> -Toloxyl	151-153	62	1-10
28.	Thymyloxy	223.5-225	78	1-10
29.	Carvacryloxy	175-176	67	0
30.	3-Methyl-4-chlorophenoxy	221-223	57	10
31.	<i>o</i> -Isopropylphenoxy	173.5-174.5	58	10
32.	2,5-Dimethylphenoxy	223.5-225.5	67	10

* γ of compound per milliliter of bath liquid, capable of neutralizing the contraction of an isolated guinea-pig gut caused by 1 γ /ml. of histamine diphosphate.

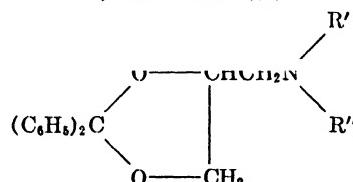
TABLE 11
Aryloxyalkylimidazolines



NO.	R	MELTING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
1....	(C ₆ H ₅) ₂ CHOCH ₂ —	102-103	203-205 (HCl) 204 (picrate)	(70, 71, 104, 114, 328)
2....	(C ₆ H ₅) ₂ CHOCH ₂ CH ₂ CH ₂ —		218 (HCl)	(70)
3....	(C ₆ H ₅) ₂ CHOCH(C ₂ H ₅)		218 (HCl)	(70)
4....	p-CH ₃ C ₆ H ₄ CHOCH ₂ — C ₆ H ₅	99	189 (HCl)	(102)
5....	p-CH ₃ O C ₆ H ₄ CHOCH ₂ CH ₂ — C ₆ H ₅	87	150 (HCl) 152 (dioxalate) 151 (picrate)	(102)
6....	C ₆ H ₅ CH ₂ OCH ₂ —	58	161 (HCl) 153 (picrate)	(328)
7....	C ₆ H ₅ CH ₂ CH ₂ OCH ₂ —		128 (HCl) 121 (picrate)	(328)
8....	p-CH ₃ O C ₆ H ₄ CHOCH ₂ — C ₆ H ₅	87	180 (HCl) 145 (dioxalate) 132 (picrate)	(102)
9....	C ₆ H ₅ CH ₂ CH ₂ CH ₂ OCH ₂ —		51 (HCl) 168 (picrate)	(328)
10....	C ₆ H ₅ SCH ₂ —	85	185 (HCl) 128 (picrate)	(328)
11....	p-C ₆ H ₅ C ₆ H ₄ OCH ₂ —		225 (HCl)	(70)
12....	o-C ₆ H ₅ C ₆ H ₄ OCH ₂ —		225 (HCl)	(70)
13....	o-C ₆ H ₅ C ₆ H ₄ OCH ₂ —		116 (HCl)	(70)
14....	 CHOCH ₂ — C ₆ H ₄ OCH ₃ -p		205 (HCl) 126 (dioxalate)	(102)

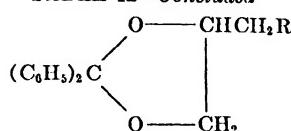
TABLE 11—Concluded

NO.	R	MELTING POINT °C.	MELTING POINT OF SALT °C.	REFERENCES
15	 $\text{C}_6\text{H}_4\text{OCH}_3\text{-}p$		156 (dioxalate) 179 (picrate)	(103)
16	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CHOCH}_2\text{-}$ 		198 (dioxalate)	(103)

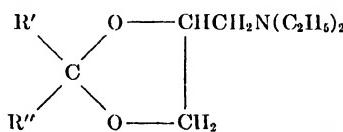
TABLE 12
1,3-Dioxolanes (48)

NO.	R'	R''	SALT	ANTIHISTAMINE ACTIVITY*
				$\mu\text{g./ml.}$
1.	H	H	HCl	
2.	H	CH ₃	HCl	2
3.	CH ₃	CH ₃	HCl	5
4.	CH ₃	CH ₃	CH ₃ Br	5
5.	CH ₃	CH ₃	CH ₃ I	1
6.	C ₂ H ₅	C ₂ H ₅	HCl	0.5
7.	H	i-C ₄ H ₉	HCl	5
8.	n-C ₃ H ₇	n-C ₃ H ₇	HCl	10
9.	n-C ₄ H ₉	n-C ₄ H ₉	HBr	720

TABLE 12—Concluded



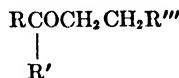
NO.	R	SALT	ANTIHISTAMINE ACTIVITY*
10.	—OCH ₂ CH ₂ N(C ₂ H ₅) ₂	HCl	μg./ml. 0.1
11.	—N(—C ₆ H ₅) ₂	HCl	1
12.	—N(—C ₆ H ₅) ₂	CH ₃ I	5
13.	—N(—C ₆ H ₅) ₂ O	HCl	20



NO.	R'	R''	SALT	ANTIHISTAMINE ACTIVITY*
14.	Phenyl	α-Thienyl	HCl	μg./ml.
15.	α-Thienyl	α-Thienyl	HCl	5
16.	p-Tolyl	p-Tolyl	HCl	5
17.	p-Tolyl	p-Tolyl	CH ₃ I	10
18.	p-Chlorophenyl	p-Chlorophenyl	HCl	5
19.	p-Methoxyphenyl	p-Methoxyphenyl	HCl	2
20.	Diphenylmethyl	Hydrogen	HCl	5
21.	Cyclopentamethylene		HCl	>20
22.	Cyclopentamethylene		CH ₃ I	>20
23.	o-Diphenylene		HBr	10

* Minimum effective concentration to antagonize 0.2 μg./ml. of histamine (isolated guinea-pig intestine) in micrograms per milliliter.

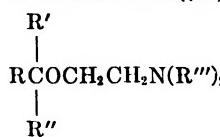
TABLE 13
Miscellaneous cyclic ethers (463)
 R''



NO.	R	R'	R''	R'''	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY*
1...	C ₆ H ₅ —		H	—N(CH ₃) ₂	133/0.25 mm.	120 (HCl) 177 (CH ₃ I)	0.4 0.3
2...	C ₆ H ₅ —		H	—N	181/0.5 mm.	134 (CH ₃ I)	0.14–0.25
3...	C ₆ H ₅ —		H	—N(CH ₃) ₂	123/0.25 mm.	138 (HCl)	0.06
4...	C ₆ H ₅ —		H	—N		153 (HCl)	0.07–0.14
5..	C ₆ H ₅ —	C ₆ H ₅ CH ₂ —	H	—N(CH ₃) ₂	131/0.35 mm.	133 (HCl)	0.04
6...	C ₆ H ₅ —	C ₆ H ₅ CH ₂ —	H	—N	196/0.7 mm.	114 (HCl)	0.03
7...	n-C ₄ H ₉	n-C ₄ H ₉	H	—N	125/2.3 mm.		0.3
8...	p-CH ₃ OC ₆ H ₄ —	p-CH ₃ OC ₆ H ₄ CH ₂ —	H	—N	219/0.35 mm.	144 (HCl)	0.07

* Antihistaminic activity in terms of Benadryl = 1.

TABLE 14
Alkamine ethers (405)



NO.	R	R'	R''	R'''	YIELD per cent	BOILING POINT
						°C.
1....	2-C ₆ H ₄ N—*	C ₆ H ₅ —	H	CH ₃	82	158-162/1.5 mm.
2....	3-C ₆ H ₄ N—	C ₆ H ₅ —	H	CH ₃	69	149-153/1 mm.
3....	2-C ₆ H ₄ N—	p-i-C ₃ H ₇ C ₆ H ₄ —	H	CH ₃	84	165-167/0.5 mm.
4....	2-C ₆ H ₄ N—	p-CH ₃ C ₆ H ₄ —	H	CH ₃	88	156-160/1 mm.
5....	2-C ₆ H ₄ N—	m-CH ₃ C ₆ H ₄ —	H	CH ₃	72	155-159/0.5 mm.
6....	2-C ₆ H ₄ N—	p-CH ₃ OCC ₆ H ₄ —	H	CH ₃	86	168-172/0.5 mm.
7....	2-C ₆ H ₄ N—	p-(CH ₃) ₂ NCC ₆ H ₄ —	H	CH ₃	61	168-172/2.5 mm.
8....	2-C ₆ H ₄ N—	3,4-(—OCH ₂ O—)C ₆ H ₃ —	H	CH ₃	45	176-180/1 mm.
9....	2-C ₆ H ₄ N—	o-ClC ₆ H ₄ —	H	CH ₃	28	152-156/2 mm.
10....	2-C ₆ H ₄ N—	p-ClC ₆ H ₄ —	H	CH ₃	47	164-167/2 mm.
11....	2-C ₆ H ₄ N—	C ₆ H ₅ CH ₂ —	H	CH ₃	63	138-142/0.5 mm.
12....	2-C ₆ H ₄ N—	C ₆ H ₅ CH ₂ CH ₂ —	H	CH ₃	56	178-180/0.5 mm.
13....	2-C ₆ H ₄ N—	2-C ₆ H ₅ S—†	H	CH ₃	22	145/1 mm.
14....	2-C ₆ H ₄ N—	n-C ₃ H ₇	H	CH ₃	47	103-105/0.2 mm.
15....	2-C ₆ H ₄ N—	C ₆ H ₅ —	H	C ₂ H ₅	82	147-150/0.5 mm.
16....	2-C ₆ H ₄ N—	p-CH ₃ C ₆ H ₄ —	H	C ₂ H ₅	50	162-165/1 mm.
17....	2-C ₆ H ₄ N—	p-CH ₃ OCC ₆ H ₄ —	H	†	70	143-147/0.5 mm.
18....	3-C ₆ H ₄ N—	C ₆ H ₅ —	CH ₃	CH ₂	87	160-161/1.5 mm.
19....	2-C ₆ H ₄ N—	C ₆ H ₅ —	CH ₃	CH ₃ §	46	137-141/0.5 mm.
20....	2-C ₆ H ₄ N—	p-ClC ₆ H ₄ —	CH ₃	CH ₃	66	155-159/1 mm.
21....	3-C ₆ H ₄ N—	C ₆ H ₅ CH ₂ —	CH ₃	CH ₃	76	170-173/1 mm.

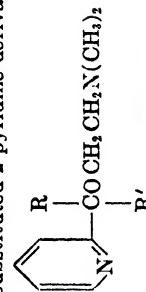
* Pyridyl.

† 2-Phenyl.

‡ Either (CH₃)₂NCH₂CH— or (CH₃)₂NCHCH₂— or both.

§ Decapryl.

TABLE 15
Pyridine derivatives (423)
 A. Substituted 2-pyridine derivatives



No.	R	R'	BOILING POINT °C.	YIELD per cent	MELTING POINT OF SALT °C.	ANTISESTAMINE ACTIVITY	
						γ/ml.	
1	Phenyl	H	147-151/0.3 mm.	74	103-105 (HCl)	0.05	
2	α-Methylbenzyl	H	148-152/0.2 mm.	7	144-146 (HCl)	1.0	
3	p-Cumyl	H	159-163/0.1 mm.	73	122-123 (HCl)	0.5	
4	o-Anisyl	H	152-154/0.2 mm.	46	133-135 (HCl)	5.0	
5	3,4-Methylenedioxypyhenyl	H	182-185/0.1 mm.	75	147-149 (HCl)	2.0	
6	2-Chlorophenyl	CH ₃	174-176/0.15 mm.	43	116-118 (HCl)	1.0	
7	Phenyl	CH ₃	145-153/0.4 mm.	75	169-170 (HCl)	0.05	
8	Benzyl	CH ₃	146-155/0.3 mm.	75	118-120 (2HBr)	5.0	
9	p-Tolyl	CH ₃	145-153/0.2 mm.	53	178-179 (HCl)	0.05	
10	o-Tolyl	CH ₃	160-162/0.1 mm.	31	172-174 (HCl)	5.0	
11	m-Tolyl	CH ₃	152-156/0.1 mm.	44	134-136 (HCl)	0.5	
12	3,4-Xylyl	CH ₃	162-164/0.08 mm.	58	152-154 (HCl)	1.0	
13	Carvacyryl	CH ₃	160-165/0.15 mm.	42	184-186 (HCl)	5.0	
14	α-Naphthyl	CH ₃	185-195/0.3 mm.	56	229-230 (HCl)	5.0	
15	β-Naphthyl	CH ₃	185-195/0.2 mm.	50	161-162 (HCl)	5.0	
16	m-Anisyl	CH ₃	167-173/0.2 mm.	60	130-132 (HCl)	0.05	
17	p-Anisyl	CH ₃	173-175/0.2 mm.	67	152-153 (HCl)	0.1	
18	3,4-Dimethoxyphenyl	CH ₃	175-180/0.2 mm.	52	174-175 (HCl)	20.0	
19	3-Chlorophenyl	CH ₃	158-162/0.1 mm.	58	137-138 (HCl)	0.1	
20	4-Chlorophenyl	CH ₃	154-156/0.2 mm.	60	162-164 (HCl)	0.1	
21	3-Bromophenyl	CH ₃	180-185/0.2 mm.	39	126-128 (HCl)		

No.	P	R'	BOILING POINT °C.	YIELD per cent	MELTING POINT OF SALT °C.	ANTIHISTAMINE ACTIVITY	
						γ/ml.	
22 . . .	Phenyl	C ₂ H ₅ , C ₃ H ₇ , —CH ₂ CH ₂ N(CH ₃) ₂	150-153/0.09 mm. 153-162/0.1 mm.	34	201-202 (HCl)	0.5	
23 . . .	Phenyl	Phenyl	180-188/0.3 mm.	34	161-163 (HCl)	5.0	
24 . . .	Phenyl	Benzyl	175-180/0.25 mm.	26	244-245 (2HBr)	1.0	
25 . . .	Phenyl	CH ₃	138-142/0.2 mm.	40	186-187 (HCl)	1.0	
26 . . .	Benzyl	CH ₃	128-132/0.2 mm.	32	267-268 (2HCl)	20.0	
27 . . .	1-Cyclohexenyl	CH ₃	95-102/0.28 mm.	25	136-138 (HCl)	0.1	
28 . . .	Cyclohexyl	CH ₃	138-143/0.3 mm.	35	164-165 (HCl)	3.0	
29 . . .	Cyclopropyl	CH ₃	95-103/0.3 mm.	28	95-97 (HCl)	10.0	
30 . . .	n-Hexyl	i-C ₄ H ₉ —CH ₂ CH ₂ CH ₂ N(CH ₃) ₂	155-160/0.23 mm.	19	65-96 (HCl)	5.0	
31 . . .	CH(CH ₃) ₂	CH ₃	155-160/0.23 mm.	41	187-188 (HCl)	10.0	
32 . . .	CH ₃	CH ₃	155-158/0.5 mm.	10	191-192 (3HCl)	20.0	
33 . . .	2-Pyridyl	CH ₃			154-156 (3HBr)	1.0	
34 . . .	2-Thienyl	CH ₃			119-120 (HCl)	10.0	

B. Cyclic 2-pyridine derivatives



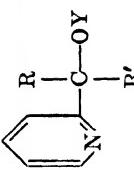
No.	R	BOILING POINT °C.	YIELD per cent	MELTING POINT OF SALT °C.	ANTIHISTAMINE ACTIVITY	
					γ/ml.	
35 . . .	Cyclohexyldene	139-142/1.0 mm.	14	163-164 (2HCl)	20.0	
36 . . .	d-Bornyldene	133-138/0.2 mm.	48	146-148 (2HCl)	5.0	
37 . . .	d-Fenchylidene	135-138/0.2 mm.	61	197-198 (HCl)	1.0	
38 . . .	1-Indanylidene	162-164/0.3 mm.	28	137-139 (HCl)	5.0	

TABLE 15—Continued
C. 2, 3, and 4-Pyridine derivatives



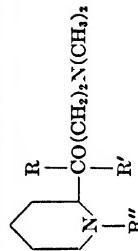
NO.	R	R'	R''	BOILING POINT °C.	YIELD per cent	MELTING POINT OF SALT °C.	ANTIHISTAMINE ACTIVITY*	
39	3-Pyridyl	Phenyl	H	160-165/0.2 mm.	55	79-81 (HBr)		
40	4-Pyridyl	Phenyl	H	145-148/0.2 mm.	32	103-105 (HCl)	0.5	
41	4-Pyridyl	Phenyl	CH ₃	158-160/0.3 mm.	51	282.5-284.5 (2HCl)	20.0	
42	(2-Pyridyl)methyl	Phenyl	H	150-160/0.5 mm.	7	152-154 (2HBr)	5.0	
43	2-(4-Picoly)	Phenyl	CH ₃	152-156/0.1 mm.	66	162-164 (HCl)	1.0	
44	2-(6-Picoly)	Phenyl	CH ₃	145-150/0.3 mm.	30	153-155 (HCl)	0.1	

D. Variation of side chain



No.	R	R'	Y	BOILING POINT °C.	YIELD per cent	MELTING POINT OF SALT °C.	ANTIHISTAMINE ACTIVITY*
							per cent
45.....	Phenyl	CH ₃	-C ₂ H ₄ N(CH ₃) ₂ -2CH ₃ I	47	143-144 (HCl)	20.0	
46.....	Phenyl	CH ₃	-C ₂ H ₄ N(CH ₃) ₂ -HOCH ₂ H ₄ Cl	75	73-75 (HCl)	0.5	
47.....	Phenyl	CH ₃	-C ₂ H ₄ N(CH ₃) ₂	150-156/0.2 mm.	73	109-111 (HBr)	0.5
48.....	Phenyl	CH ₃	-CH ₂ CH(CH ₃)N(CH ₃) ₂	148-151/0.05 mm.	61	147-149 (HCl)	1.0
49.....	Phenyl	CH ₃	-C ₂ H ₄ N(CH ₃) ₂ -CH ₂ CH ₂ -	160-166/0.08 mm.	68	177-179 (HCl)	0.1
50.....	Phenyl	CH ₃	-C ₂ H ₄ N(CH ₃) ₂ -CH ₂ CH ₂ -O-	168-174/0.1 mm.	61	184-186 (HCl)	1.0
51.....	Phenyl	CH ₃	-C ₂ H ₄ N(CH ₃) ₂ -CH ₂ CH ₂ -	156-162/0.1 mm.	53	145-147 (HCl)	1.0
52.....	dL-Fenchyl		-C ₂ H ₄ N(CH ₃) ₂	150-156/0.2 mm.	65	192-194 (HCl)	5.0

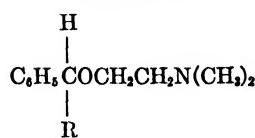
E. Substituted 2-piperidine derivatives



No.	R	R'	R"	BOILING POINT °C.	YIELD per cent	MELTING POINT OF SALT °C.	ANTIHISTAMINE ACTIVITY*
							per cent
53.....	Phenyl	Phenyl	H	150-155/0.2 mm.	40	246-246.5 (2HCl)	5.0
54.....	Phenyl	CH ₃	CH ₃	133-139/0.1 mm.	30	222-224 (2HCl)	50

* Minimum dose of test compound necessary to antagonize 0.1 µg./ml. of histamine diphosphate on isolated intestine of guinea pig.
Benadryl = 0.05.

TABLE 16



NO.	R	BOILING POINT	YIELD per cent	MELTING POINT OF SALT °C.	ANTI- HISTA- MINE ACTIV- ITY*	REFER- ENCES
1..		135-140/0.2 mm.	30	150 (HCl) 177 (2HCl)	20† 20†	(425)
2..		155-160/0.08 mm.	63	247 (2HCl)	20†	(425)
3..		100-101/0.035 mm.	39		30‡	(25)
4..	C ₆ H ₅ CH ₂ -	169-171/2-3 mm.		117 (HCl)	1.0§	(327)
FORMULA						
5..		190-195/3 mm.		124 (HCl)	0.22§	(327)
6..				144 (CH ₃ I)		(463)

* Reference 463.

† See table 15.

‡ Average per cent by which a bath concentration of 9.37×10^{-5} $\mu\text{g./ml.}$ of antihistaminic reduced the response of guinea-pig ileum to a histamine base concentration of $0.024 \mu\text{g./ml.}$ Benadryl = 17.

§ See table 4, Nos. 10 and 11.

TABLE 17
3-(N,N-Diethylamino)propyl sulfides (31)

NO.	R	BOILING POINT	YIELD	MELTING POINT OF HYDROCHLORIDE
RSCH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂				
		°C.	per cent	°C.
1.....	<i>o</i> -ClC ₆ H ₄ CH ₂ —	190-193/12 mm.	80	84
2.....	2,4-Cl ₂ C ₆ H ₃ CH ₂ —	165-168/4 mm.	73	117
3.....	3,4-Cl ₂ C ₆ H ₃ CH ₂ —	169-172/3 mm.	81	76
4.....	C ₆ H ₅ —	141-143/6 mm.	81	62
5.....	<i>o</i> -CH ₃ C ₆ H ₄ —	150-153/5 mm.	71	127
6.....	<i>m</i> -CH ₃ C ₆ H ₄ —	168-173/13 mm.	88	66
7.....	<i>p</i> -CH ₃ C ₆ H ₄ —	155-158/7 mm.	81	98
RSCH ₂ CHOHCH ₂ N(C ₂ H ₅) ₂				
8.....	<i>o</i> -ClC ₆ H ₄ CH ₂ —	190-195/4 mm.	60	
9.....	2,4-Cl ₂ C ₆ H ₃ CH ₂ —	210-215/4 mm.	66	
10.....	3,4-Cl ₂ C ₆ H ₃ CH ₂ —	210-215/4 mm.	69	
11.....	C ₆ H ₅ —	168-171/4 mm.	86	
12.....	<i>o</i> -CH ₃ C ₆ H ₄ —	154-157/1 mm.	65	
13.....	<i>m</i> -CH ₃ C ₆ H ₄ —	168-172/3 mm.	60	
14.....	<i>p</i> -CH ₃ C ₆ H ₄ —	168-172/3 mm.	64	

TABLE 18
Heterocyclic alkamine ethers (415)

NO.	FORMULA	BOILING POINT °C.	MELTING POINT OF SALT °C.
1.....		80-89/5 mm.	138 (picrate)
2.....			111 (HCl)
3.....		110-120/2 mm.	190 (HCl) 179 (picrate)
4.....			175 (HCl)
5.....		80-90/0.3 mm.	155 (dipicrate)
6.....			182 (HCl) 161 (picrate)
7.....		147-155/4 mm.	191 (HCl)
8.....		165-175/2 mm.	156 (2HCl) 153 (picrate)*

Reference 307.

TABLE 19
Alkamine ethers of benzylphenols (81)

No.	CODE NO.	R	R'	YIELD per cent	BOILING POINT AT 1 MM. PRESSURE	MELTING POINT OF HYDROCHLORIDE	°C.
1....	C-5581-H	2-Benzylphenyl	-CH ₂ CH ₂ N(CH ₃) ₂	94.3	141-144	119-120	
2....	338-20	4-Benzylphenyl	-CH ₂ CH ₂ N(CH ₃) ₂	64.5	152-153	179-182	
3....	338-19A	2-Benzylphenyl	-CH(CH ₃)CH ₂ N(CH ₃) ₂		148-152	75-80	
4....	338-19B	2-Benzylphenyl	-CH ₂ CH(CH ₃)N(CH ₃) ₂		152-157	170-171.5	
5....	338-22	2-Benzylphenyl	-CH ₂ CH ₂ N(C ₂ H ₅) ₂	76.8	160-164	158-159	
6....	546-1	2-Benzylphenyl	$\begin{array}{c} \text{CH}_2\text{CH}_2 \\ \\ -\text{CH}_2\text{CH}_2\text{CH}_2\text{N} \end{array}$ $\begin{array}{ccccc} & \diagup & \diagdown & & \\ & \text{CH}_2 & \text{CH}_2 & \text{CH}_2 & \\ & \diagdown & \diagup & & \\ & \text{CH}_2 & \text{CH}_2 & \text{CH}_2 & \end{array}$ $\begin{array}{c} \text{CH}_2 \\ \\ \text{CH}(\text{CH}_3)\text{CH}_2 \end{array}$	63.3	192-198	167-168	
7....	546-2	2-Benzylphenyl	$\begin{array}{c} \text{CH}_2\text{CH}_2\text{CH}_2 \\ \\ -\text{CH}_2\text{CH}_2\text{CH}_2\text{N} \end{array}$ $\begin{array}{c} \diagup & \diagdown \\ \text{CH}(\text{CH}_3)\text{CH}_2 \end{array}$	66.2	194.5-197	149-150	
8....	546-3	2-Benzylphenyl	-CH ₂ CH ₂ CH ₂ N(CH ₃) ₂	86.6	149-153	159-160	
9....	546-13	2-Benzylphenyl	-CH ₂ CH ₂ CH ₂ N(<i>n</i> -C ₄ H ₉) ₂	98.2	174-176	86-89	
10....	546-14	4-Benzylphenyl	-CH ₂ CH ₂ CH ₂ N(<i>n</i> -C ₄ H ₉) ₂	75	197-200	96-98	

TABLE 19—Continued

No.	Code No.	R	R'	YIELD per cent	BOILING POINT AT 1 MM. PRESSURE °C.	MELTING POINT OF HYDROCHLORIDE °C.
11....	612-9	2-Benzylphenyl	$ \begin{array}{c} \text{CH}_2\text{CH}_2 \\ \\ \text{---CH}_2\text{CH}_2\text{N} \\ \\ \text{CH}_2\text{CH}_2 \end{array} $	73.5	152-163	140-141.5
12....	612-10	2-Benzylphenyl	$ \begin{array}{c} \text{CH}_2\text{CH}_2 \\ \\ \text{---CH}_2\text{CH}_2\text{N} \\ \\ \text{CH---CH}_2 \\ \\ \text{CH}_2\text{CH}_2 \end{array} $	75.5	151-167	139.5-142
13....	380-1	2-Benzylphenyl	$ \begin{array}{c} \text{CH}_2\text{CH}_2 \\ \\ \text{---CH}_2\text{CH}_2\text{N} \\ \\ \text{CH}_2\text{CH}_2\text{O} \end{array} $	85.5		184-185
14....	380-3	2-Benzylphenyl	$ \begin{array}{c} \text{CH}_2\text{CH}_2 \\ \\ \text{---CH}_2\text{CH}_2\text{N} \\ \\ \text{CH}_2\text{CH}_2 \end{array} $	55.3	180-183	139-141
15....	489-27	2,6-Dibenzylphenyl	$ \begin{array}{c} \text{---CH}_2\text{CH}_2\text{N}(\text{CH}_2) \\ \\ \text{---CH}_2\text{CH}_2\text{N}(\text{CH}_2) \end{array} $	31.5		143-144.5

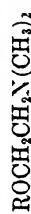
16.....	489-2	Hexahydro-2-benzylphenyl	$-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	25.7	170
17.....	489-1	2-Cyclohexylmethylecyclohexyl	$-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	38	128.5-129
18.....	489-9	2-Benzylphenyl	$-\text{CH}_2\text{CH}_2\text{NHCH}(\text{CH}_3)_2$	81.2	174-175
19.....	489-10	2-Benzylphenyl	$-\text{CH}_2\text{CH}_2\text{NHCH}_3$	22.3	178.5-179.5
20.....	518-14	2-Benzylphenyl	$ \begin{array}{c} \text{CH}_2\text{CH}_2 \\ \\ -\text{CH}_2\text{CH}_2\text{NHCH} \\ \\ \text{CH}_2\text{CH}_2 \\ \\ \text{CH}_2\text{CH}_2 \end{array} $	34.8	182-183.5
				165-171	

Substituted 2-benzylphenyl 2-dimethylaminoethyl ethers (453)
 $\text{ROCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$

No.	Code No.	R	Yield Percent	Boiling Point °C.	MELTING POINT OF HYDROCHLORIDE °C.
21.....	446-24	2-Benzyl-1-tolyl	89	163-174/3 mm.	126.5-128.0
22.....	480-6	4- <i>tert</i> -Butyl-2-benzylphenyl	87	137-140/1 mm.	162.5-164.0
23.....	446-44	4-Cyclohexyl-2-benzylphenyl	87	186-190/1 mm.	152.5-154.0
24.....	446-15	4-Methoxy-2-benzylphenyl	86	174-177/1 mm.	131.0-132.0
25.....	446-28	4-Ethoxy-2-benzylphenyl	79	167-171/1 mm.	136.0-137.0
26.....	446-21	4-Chloro-2-benzylphenyl	82	172-176/1 mm.	173.5-175.5
27.....	551-43	6-Chloro-2-benzylphenyl	76	160-164/1 mm.	93.0-95.0
28.....	480-25	2-(4'-Isopropylbenzyl)phenyl	90	151-152/1 mm.	144.0-145.5
29.....	446-34	2-(4'-Methoxybenzyl)phenyl	89	149-152/1 mm.	123.0-126.0
30.....	480-38	2-(2',3'-Dimethoxybenzyl)phenyl	90	164-166/1 mm.	
31.....	518-35	2-(2',2'-Chlorobenzyl)phenyl	80	155-167/1 mm.	139.5-142.5
32.....	551-13	2-(3',2'-Chlorobenzyl)phenyl	82	146-152/1 mm.	120.0-121.5
33.....	446-48	2-(4'-Chlorobenzyl)phenyl	81	179-185/3 mm.	152.0-153.0
34.....	570-26	2-(4'-Bromobenzyl)phenyl	92	162-165/1 mm.	158.0-160.5
35.....	518-39	4-Chloro-2-(4'-chlorobenzyl)phenyl	86	177-182/1 mm.	150.0-152.0
36.....	570-31	2-(2',4'-Dichlorobenzyl)phenyl	91	149-152/1 mm.	139.5-141.0

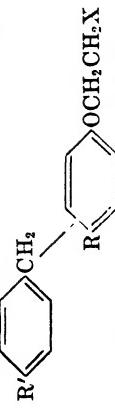
TABLE 19—Continued

NO.	CODE NO.	R	YIELD per cent	BORING POINT °C.	MELTING POINT OF HYDROCHLORIDE °C.
37.....	570-35	4,6-Dichloro-2-benzylphenyl	85	159-163/1 mm.	137.5-140.5
38.....	490-12	2-Benzoylphenyl	95	180-181/1 mm.	144.0-145.5
39.....	490-15	2-(α -Hydroxybenzyl)phenyl	70	142-146/1 mm.	153.0-154.0
40.....	518-49	2-(α -Methylbenzyl)phenyl	78	189-192/1 mm.	141.0-142.5
41.....	518-19	2-Benzhydrylphenyl	88	184.0-186.5	



NO.	R	YIELD per cent	BORING POINT °C.	MELTING POINT OF HYDROCHLORIDE °C.
42.....	2-Methoxy-6-benzylphenyl	83	144-148/1 mm.	92.5-94.0
43.....	4-Bromo-2-benzylphenyl	89	164-167/1.5 mm.	179.5-181.0
44.....	4-Iodo-2-benzylphenyl	73		167.0-170.0
45.....	4-Fluoro-2-benzylphenyl	89	131-134/1 mm.	124.5-125.5
46.....	4-Dimethylamino-2-benzylphenyl	73	171-186/1 mm.	154.0-156.0
47.....	2-(4'-Fluorobenzyl)phenyl	72	140-146/2 mm.	131.0-132.5
48.....	2-Cinnamylphenyl	82	137-141/1 mm.	154.0-156.5
49.....	2-(2'-Phenyl)phenyl	76	159-160/1 mm.	129.0-130.0
50.....	2-(5'-Chloro-2'-phenyl)phenyl	86	149-150/1 mm.	103.0-106.0
51.....	1-Benzyl-2-naphthyl	88	184-192/1.5 mm.	178.0-181.0
52.....	2-Benzyl-1-naphthyl	79	200-207/2 mm.	183.5-185.5
53.....	1-Allyl-2-naphthyl	87	139-143/1 mm.	151.0-152.5
54.....	2-Allyl-1-naphthyl	79	136-145/1 mm.	
55.....	7-Benzyl-8-quinolyl	86	190-197/1 mm.	205.0-207.0

2-(Benzylphenoxy)ethyl halides (456)



No.	R	R'	X	POSITION OF BENZYL GROUP	YIELD per cent	BOILING POINT °C.	MELTING POINT °C.	
							Ortho	Ortho
56	H	H	Cl	Ortho	89			65.0-66.0
57	H	H	I	Ortho	88			95.0-98.0
58		H	Cl	Para	94			64.0-65.0
59		H	Cl	Ortho	91	148/1 mm.		
60		H	Cl	Ortho	98		46.5-48.5	
61		H	F	Ortho	97	144-147/2 mm.		

2-Chloroethylamines



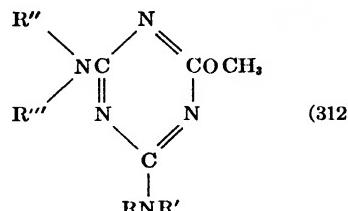
No.	R	R'	R''	R'''	YIELD per cent	MELTING POINT OF HYDROCHLORIDE °C.	
						R'	per cent
62	H	H	-CH ₃	H	78	118	
63	H	H	-C ₂ H ₅	H	71	163	
64	H	H	-CH(CH ₃) ₂	H	78	139	
65	H	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	76	111	
66	H	H	-CH(CH ₃)C ₂ H ₅	H	63	110	
67	H	H	-CH ₂ CH(CH ₃) ₂	H	80	103	

TABLE 19—Concluded

NO.	R	R'	R''	R'''	YIELD per cent	MELTING POINT OF HYDROCHLORIDE °C.
						MELTING POINT OF HYDROCHLORIDE °C.
68.....	H	H	-CH ₂ CH(C ₂ H ₅)C ₄ H ₉ -CH ₂ C ₄ H ₉	H	72	84
69.....	H	H		H	67	153
70.....	H	H		H	87	110
71.....	H	H	-CH(CH ₃)CH ₂ C ₄ H ₉	H	73	155
72.....	H	H	-CH ₂ CH ₂ Cl	H	54	158
73.....	H	H	-CH(CH ₃) ₂	CH ₃	61	118
74.....	H	H	-CH(CH ₃) ₂	-CH=CH ₂	31	102
75.....	H	H	-CH(CH ₃) ₂	-C ₂ H ₅	62	127
76.....	H	Cl	-CH(CH ₃) ₂	H	69	133
77.....	Cl	H	-CH(CH ₃) ₂	H	76	147
78.....	H	F	-CH(CH ₃) ₂	H	83	138
79.....	H	H	-CH(CH ₃) ₂	H	49	109

TABLE 20
Alkoxy-s-triazines (94)
 2-R-4,6-Diamino-s-triazines

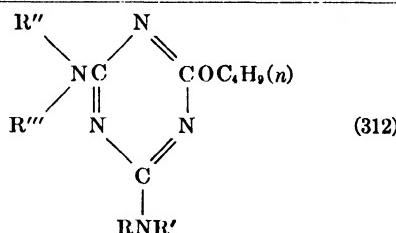
NO.	R	MELTING POINT °C.	YIELD per cent	RELATIVE ANTI-HISTAMINE ACTIVITY ^(a)
1....	Methoxy	220-230	81	1
2....	Ethoxy	182	72	2
3....	n-Propoxy	182-183	88	4
4....	Isopropoxy	172	78	4
5....	n-Butoxy	174-175	75	2
6....	Isobutoxy	186	93	4
7....	sec-Butoxy	173-174	50	4
8....	n-Pent oxy	147	28	2
9....	n-Hexaoxy	152	58	3
10....	n-Heptoxy	139	63	
11....	n-Octoxy	122-124	46	
12....	n-Noxy	115	41	
13....	n-Decoxy	121-123	29	
14....	Allyloxy	181-182	82	2
15....	2-Ethoxyethoxy	155-156	33	1
16....	2-Phenoxyethoxy	184-185	77	
17....	Cyclohexoxy	209	53	4
18....	Benzylxy	187	65	
19....	2-Dimethylaminoethoxy	122	37	
20....	3-Diethylaminoproxy	147	38	
21....	2-Morpholinoethoxy	211-212	46	
22....	Isopropylthio	190	68	4
	NAME			
23....	2-Ethoxy-1,6-di(monoisopropanolamino)-s-triazine	119-120	49	2
24....	2-Ethoxy-4-monoisopropanolamino-6-amino-s-triazine	140-142	83	
25....	2-N-Butoxy-4-monoisopropanolamino-6-amino-s-triazine	131	87	4



NO.	R	R'	R''	R'''	MELTING POINT	YIELD	ANTITHYMINE ACTIVITY (%)	
							°C.	per cent
								mg./kg.
26 .	Methyl	H	H	H	155-156	66	50	
27 .	Ethyl	H	H	H	168-170	24	25	
28 .	<i>n</i> -Propyl	H	H	H	148-150	81	12	
29 .	<i>n</i> -Butyl	H	H	H	125-127	89	> 50	
30 .	<i>n</i> -Amyl	H	H	H	(c)	86	12	
31 .	<i>n</i> -Hexyl	H	H	H	104-106	92	12	
32 .	Allyl	H	H	H	148-150	89	12	

TABLE 20—Continued

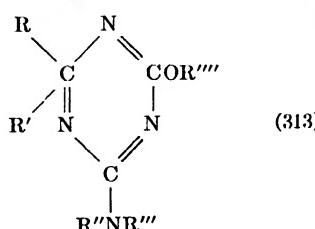
NO.	R	R'	R''	R'''	MELTING POINT °C.	YIELD per cent	ANTHIS- TAMINE ACTIV- ITY (b)
							mg./kg.
33..	Methallyl	H	H	II	129-131	88	>50
34..	Cyclohexyl	H	H	II	170-172	99	12
35..	Methyl	Methyl	H	II	169-171	81	25
36..	Ethyl	Ethyl	H	II	113-115	73	12
37..	Allyl	Allyl	H	II	87-89	83	>50
38..	Methallyl	Methallyl	H	II	101-103	90	50
39..	HOCH ₂ CH ₂ -	Ethyl	H	II	162-164	87	>50
40..	HOCH ₂ CH ₂ -	Phenyl	II	H	224-226	91	50
41..	--C ₆ H ₁₀ ^(d)	H	II	II	137-139	95	6
42..	--C ₂ H ₄ OC ₂ H ₄ ^(e)	H	II	II	182-184	80	50
43..	Methyl	H	Methyl	H	184-186	76	6
44..	Ethyl	H	Ethyl	II	81-83	46	6
45..	Allyl	H	Allyl	II	84-86	88	25
46..	Methallyl	H	Methallyl	II	112-114	93	12
47..	Methyl	Methyl	Methyl	H	187-188	80	25
48..	Ethyl	Ethyl	Ethyl	H	107-109	99	12
49..	Methyl	Methyl	Methyl	Methyl	90-92	73	25
50..	Ethyl	Ethyl	Ethyl	Ethyl	146-149/1.5 mm. ^(f)	65	50
51..	Allyl	Allyl	Allyl	Allyl	150-153/1 mm. ^(f)	93	>50
52..	Methallyl	Methallyl	Methallyl	Methallyl	151-154/1.5 mm. ^(f)	71	>50
53..	Piperidino		Piperidino		89-91	94	>50
54..	Morpholino		Morpholino		153-155	78	12



NO.	R	R'	R''	R'''	MELTING POINT °C.	YIELD per cent	ANTI- EISTA- MINE ACTIV- ITY (b)	
							mg./kg.	
55 ..	Methyl	H	H	H	173-175	88		6
56 ..	Ethyl	H	H	H	116-118	86		12
57 ..	<i>n</i> -Propyl	H	H	H	116-118	85		25
58 ..	<i>n</i> -Butyl	H	H	H	103-104	72		
59 ..	<i>n</i> -Amyl	H	H	H	107-109	81		12
60 ..	<i>n</i> -Hexyl	H	H	H	119-121	99		12
61 ..	Allyl	H	H	H	87-89	75		12

TABLE 20—Continued

	R	R'	R''	R'''	MELTING POINT	YIELD	ANTI-HISTAMINE ACTIVITY ^(b)
					°C.	per cent	mg./kg.
62 . .	Methallyl	H	H	H	106-108	79	>50
63 . .	Cyclohexyl	H	H	H	141-143	96	>50
64 . .	Methyl	Methyl	H	H	103-104	88	12
65 . .	Ethyl	Ethyl	H	H	73-75	51	50
66 . .	Allyl	Allyl	H	H	172-175/1 mm. ^(d)	65	>50
67 . .	Methallyl	Methallyl	H	H	60-62	87	>50
68 . .	HOCH ₂ CH ₂ —	Ethyl	H	H	123-125	64	>25
69 . .	HOCH ₂ CH ₂ —	Phenyl	H	H	157-159	61	>50
70 . .	—C ₆ H ₁₀ — ^(d)		H	H	115-117	87	>50
71 . .	—C ₂ H ₄ OC ₂ H ₄ — ^(e)		H	H	108-110	43	12
72 . .	Methyl	H	Methyl	H	103-104	60	12
73 . .	Ethyl	H	Ethyl	H	50-52	85	25
74 . .	Allyl	H	Allyl	H	185-190/1 mm. ^(d)	51	25
75 . .	Methallyl	H	Methallyl	H	58-60	70	
76 . .	Methyl	Methyl	Methyl	H	129-131	87	>25
77 . .	Ethyl	Ethyl	Ethyl	H	80-82	96	>50
78 . .	Methyl	Methyl	Methyl	Methyl	155-157/4 mm. ^(d)	69	>25
79 . .	Ethyl	Ethyl	Ethyl	Ethyl	164-165/4 mm. ^(d)	84	>25
80 . .	Allyl	Allyl	Allyl	Allyl	157-160/1 mm. ^(d)	93	>50
81 . .	Methallyl	Methallyl	Methallyl	Methallyl	164-167/1 mm. ^(d)	82	>25
82 . .	—C ₆ H ₁₀ — ^(d)		—C ₆ H ₁₀ — ^(d)		182-185/2 mm. ^(d)	71	>50
83 . .	—C ₂ H ₄ OC ₂ H ₄ — ^(e)		—C ₂ H ₄ OC ₂ H ₄ — ^(e)		117-119	66	>25



NO.	R, R'	R'', R'''	R''''	MELTING POINT	YIELD	ANTIHISTAMINE ACTIVITY ^(b)
				°C.	per cent	mg./kg.
84 . .	H, H	H, H	C ₆ H ₁₁ ^(g)	181-183	30	25
85 . .	H, H	H, H	C ₆ H ₁₁ ^(h)	170-172	30	50
86 . .	H, H	H, CH ₃	C ₂ H ₅	170-171	79	12.5
87 . .	H, H	H, CH ₃	n-C ₃ H ₇	175-177	68	12.5
88 . .	H, H	H, CH ₃	n-C ₆ H ₁₃	166-168	75	>50

TABLE 20—*Concluded*

NO.	R, R'	R'', R'''	R''''	MELTING POINT °C.	YIELD per cent	ANTIHISTAMINE ACTIVITY (b)
						mg./kg.
89 . . .	H, H	H, CH ₃	n-C ₆ H ₁₁	232-234	64	12.5
90 . . .	H, H	H, CH ₃	Phenyl	211-213	64	>25
91 . . .	H, CH ₃	H, CH ₃	C ₂ H ₅	171-173	61	12.5
92 . . .	H, H	(CH ₃) ₂	C ₂ H ₅	156-158	88	25
93 . . .	H, CH ₃	(CH ₃) ₂	C ₂ H ₅	173-175	80	25
94 . . .	H, C ₂ H ₅	(CH ₃) ₂	Cyclo-C ₆ H ₁₁	154	75	>25
95 . . .	H, H	H, C ₆ H ₁₁	C ₂ H ₅	102-105	55	>25
96 . . .	H, H	H, C ₆ H ₁₁	n-C ₃ H ₇	92-95	46	
97 . . .	H, C ₂ H ₅	H, C ₂ H ₅	C ₂ H ₅	116-118	44	>25
98 . . .	H, C ₂ H ₅	H, C ₂ H ₅	n-C ₃ H ₇	82-84	88	
99 . . .	H, H	C ₂ H ₅ O ⁽ⁱ⁾ , C ₆ H ₅	C ₂ H ₅	194-196	83	50

(a) Antihistamine activity compared to aminophylline = 1.

(b) Dose of compound in milligrams per kilogram intraperitoneally allowing survival of 50 per cent of histamine-shocked guinea pigs. The comparable dose for aminophylline is 50 and for Benadryl is 1.5.

(c) Sinters at 98-104°C.

(d) Piperidino.

(e) Morpholino.

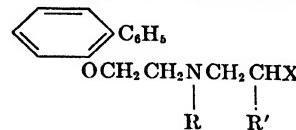
(f) Boiling point.

(g) 3-Methylbutyl.

(h) 2-Methylbutyl.

(i) Hydroxyethyl.

TABLE 21
2-(2-Biphenyloxy)ethyl-2-haloalkylamines (864)



NO.	R	R'	X	MELTING POINT OF HYDRO- CHLORIDE	ANTIHISTAMINE ACTIVITY*
				°C.	mg./kg.
1.....	C ₃ H ₇	H	Cl	166	12.5
2.....	CH ₃	H	Cl	170	1.5
3.....	C ₂ H ₅	H	Cl	166	6.0
4.....	C ₂ H ₅	H	Br		
5.....	i-C ₃ H ₇	H	Cl	133	>12.5
6.....	CH ₂ =CHCH ₂ -	H	Cl	127	>12.5
7.....	C ₄ H ₉	H	Cl	118	>25.0
8.....	i-C ₄ H ₉	H	Cl	156	
9.....	i-C ₄ H ₉	H	Br		
10.....	sec-C ₄ H ₉	H	Cl	158	
11.....	C ₅ H ₁₁	H	Cl	115	>12.5
12.....	C ₄ H ₁₃	H	Cl	102	>25.0
13.....	C ₂ H ₅	CH ₃	Cl	160	
14.....	C ₃ H ₇	CH ₃	Br		
15.....	CH ₂ =CHCH ₂ -	H	Br		
16.....	C ₂ H ₅	H	H		

NO.	FORMULA	ANTIHISTAMINE ACTIVITY*
		mg./kg.
17.....	$ m\text{-C}_6\text{H}_5\text{C}_6\text{H}_4\text{OCH}_2\text{CH}_2\text{NCH}_2\text{CH}_2\text{Cl} $ $ \qquad \qquad \qquad \downarrow \text{C}_2\text{H}_5 $	
18.....	$ \text{H}_2 \\ \\ \text{H}_2\text{C}_6\text{H}_4\text{C}_6\text{H}_4\text{OCH}_2\text{CH}_2\text{NCH}_2\text{CH}_2\text{Cl} $ $ \qquad \qquad \qquad \downarrow \text{C}_2\text{H}_5 $	>25
19.....	$ p\text{-C}_6\text{H}_5\text{C}_6\text{H}_4\text{OCH}_2\text{CH}_2\text{CH}_2\text{NCH}_2\text{CH}_2\text{Cl} $ $ \qquad \qquad \qquad \downarrow \text{C}_2\text{H}_5 $	
20.....	$ o\text{-C}_6\text{H}_5\text{C}_6\text{H}_4\text{OCH}_2\text{CH}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{Cl} $ $ \qquad \qquad \qquad \downarrow \text{C}_2\text{H}_5 $	12.5

* Diminution of histamine-induced bronchospasm in guinea pigs. Minimum effective dose subcutaneously.

TABLE 22
Fourneau amines (407)

CODE NO.	FORMULA	TOXICITY TO RABBITS		ANTIHISTAMINE INDEX‡
		M.T.D.*	M.L.D.†	
F 1167 . . .	C ₆ H ₅ NHCH ₂ CH ₂ N(C ₂ H ₅) ₂	0.015	0.05	1
F 1332 . . .	<i>o</i> -CH ₃ C ₆ H ₄ NHCH ₂ CH ₂ N(C ₂ H ₅) ₂	0.005	0.03	1
F 1335 . . .	C ₆ H ₅ NCH ₂ CH ₂ N(C ₂ H ₅) ₂ CH ₃	0.01	0.04	1.5
F 1540 . . .	C ₆ H ₅ NHCH ₂ CH ₂ NH ₂			Inactive
F 1551 . . .	C ₆ H ₅ NCH ₂ CH ₂ NH ₂ C ₂ H ₅	0.02	0.06	1
F 1571 . . .	C ₆ H ₅ NCH ₂ CH ₂ N(C ₂ H ₅) ₂ C ₂ H ₅	0.005	0.02	4
F 1590 . . .	C ₆ H ₅ N(CH ₂ CH ₂ NH ₂) ₂			Inactive (also with hydroxyl groups in <i>o</i> -, <i>m</i> -, and <i>p</i> -positions)
F 1599 . . .	<i>o</i> -CH ₃ C ₆ H ₄ NCH ₂ CH ₂ N(C ₂ H ₅) ₂ C ₂ H ₅	0.005	0.02	2
F 1656 . . .	CH ₃ NHC ₆ H ₄ CH ₂ CH ₂ N(C ₂ H ₅) ₂ CH ₃	0.005	0.03	2
F 1670 . . .	CH ₃ N CH ₂ CH ₂ N(C ₂ H ₅) ₂ C ₂ H ₅ CH ₃	0.0025	0.02	1.5
F 1691 . . .	CH ₃ NHCH ₂ CH ₂ N(C ₂ H ₅) ₂ CH(CH ₃) ₂	0.01	0.02	3

TABLE 22—*Concluded*

CODE. NO.	FORMULA	TOXICITY TO RABBITS		ANTIHISTAMINE INDEX†
		M.T.D.*	M.L.D.†	
F 1699....		0.0025	0.015	1
F 1709....		0.002	0.015	3
F 1718....		0.0025	0.025	1

* Maximum tolerated dose.

† Minimum lethal dose.

‡ Antihistamine index (histamine shock).

TABLE 23
Isocyclic diamines prepared by Fournau and Lestrange (144)

NO.	R	R'	BOILING POINT	MELT- ING POINT	MELTING POINT OF SALT
$\begin{array}{c} \text{RNCH}_2\text{CH}_2\text{NH}_2 \\ \\ \text{R}' \end{array}$					
1 (F 1540)*	C ₆ H ₅ —	H	143–145/15 mm.		205 (HCl) 187 (2HCl)
2.....	C ₆ H ₅ —	CH ₃			205 (2HCl)
3 (F 1551)*	C ₆ H ₅ —	C ₂ H ₅	134–135/15 mm.		201 (HCl) 237 (2HCl)
4.....	p-CH ₃ C ₆ H ₄ —	H	150/15 mm.	110	249 (HCl)
5.....	o-CH ₃ C ₆ H ₄ —	H	157–160/15 mm.		200 (HCl)
6.....	m-CH ₃ C ₆ H ₄ —	H	168/28 mm.		213 (HCl)
7.....	2-CH ₃ -5-i-C ₃ H ₇ C ₆ H ₃ —	H	122–128/0.96 mm.		222 (HCl)
8.....	p-C ₆ H ₅ C ₆ H ₄ —	H			284 (HCl)
9.....	o-C ₆ H ₅ C ₆ H ₄ —	H	155–157/1.2 mm.	69.5	225 (HCl)
10.....	p-CH ₃ OC ₆ H ₄ —	H		64	228 (HCl) 218 (2HCl) 160 (pic- rate)
11.....	p-CH ₃ OC ₆ H ₄ —	C ₂ H ₅		125	189 d. (2HCl)
12.....	o-CH ₃ OC ₆ H ₄ —	H			206 (HCl) 178 (2HCl)
13.....	m-CH ₃ OC ₆ H ₄ —	H	188/24 mm.	46	184 (HCl) 163 d. (2HCl) 166 (pic- rate)
14.....	3,4-(CH ₃ O) ₂ C ₆ H ₃ —	H	212/24 mm.		172 (HCl) 192 d. (2HCl) 95–100 (picrate)
15.....	p-HOC ₆ H ₄ —	H	230/25 mm.	115	181 (HCl) 242 (2HCl)
16.....	p-HOC ₆ H ₄ —	—CH ₂ CH ₂ NH ₂			227 (3HCl)
17.....	p-HOC ₆ H ₄ —	C ₂ H ₅			194 (2HCl)
18.....	o-HOC ₆ H ₄ —	H			165 (2HCl)
19.....	m-HOC ₆ H ₄ —	H		131	200 (2HCl) 159 (pic- rate)
20.....	3,4-(HO) ₂ C ₆ H ₃ —	H			212 (2HCl)
21.....	m-O ₂ NC ₆ H ₄ —	H			200 (2HCl)
22.....	m-H ₂ NC ₆ H ₄ —	H			242 (3HCl)

TABLE 23—Continued

NO.	R	R'	BOILING POINT °C.	MELTING POINT °C.	MELTING POINT OF SALT °C.
23.....	2-C ₁₀ H ₇ —	H			
24.....	<i>o</i> -O ₂ NC ₆ H ₄ —	H	205/17 mm.		260 (HCl)
25.....	<i>o</i> -H ₂ NC ₆ H ₄ —	H			261 (HCl)
26.....	<i>p</i> -O ₂ NC ₆ H ₄ —	H		144	233 (HCl)
27.....	<i>p</i> -H ₂ NC ₆ H ₄ —	H			212 (2HCl)
					195 (HCl)
					269 (3HCl)



R'

NO.	R	R'	BOILING POINT °C.	MELTING POINT °C.	MELTING POINT OF SALT °C.
28.....	C ₆ H ₅ —	H	158/17 mm.		
29.....	<i>p</i> -HOC ₆ H ₄ —	H			250 (2HCl)
30.....	3,4-(HO) ₂ C ₆ H ₃ —	H			240 (2HCl)

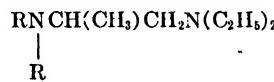


R'

NO.	R	R'	BOILING POINT °C.	MELTING POINT OF SALT °C.
31 (F 1167)*	C ₆ H ₅ —	H		135 (HCl)
32 (F 1335)*	C ₆ H ₅ —	CH ₃	190/22 mm.	114 (HCl)
33 (F 1571)*	C ₆ H ₅ —	C ₂ H ₅	152/14 mm.	166 (2HCl)
			159-161/18 mm.	147 (picrate)
34 (F 1709)*	C ₆ H ₅ —	<i>i</i> -C ₃ H ₇	147-149/13 mm.	132 (HCl)
35.....	<i>p</i> -CH ₃ C ₆ H ₄ —	H	188/20 mm. 179/15 mm.	
36.....	<i>p</i> -CH ₃ C ₆ H ₄ —	C ₂ H ₅	160-163/15 mm.	111 (HCl)
37 (F 1599)*	<i>o</i> -CH ₃ C ₆ H ₄ —	C ₂ H ₅	150-155/22 mm.	90 (HCl)
38.....	<i>m</i> -CH ₃ C ₆ H ₄ —	C ₂ H ₅	165-166/20 mm.	111 (HCl)
39.....	3,5-(CH ₃) ₂ C ₆ H ₃ —	H	171-172/15 mm.	168 (HCl)
40 (F 1670)*	2,5-(CH ₃) ₂ C ₆ H ₃ —	C ₂ H ₅	147-150/15 mm.	139 (HCl)
41.....	2,4-(CH ₃) ₂ C ₆ H ₃ —	C ₂ H ₅	155-160/15 mm.	100 (HCl)
42 (F 1718)*	<i>p</i> - <i>i</i> -C ₃ H ₇ C ₆ H ₄ —	H	175-180/15 mm.	125 (HCl)
43 (F 1691)*	2-CH ₃ -5- <i>i</i> -C ₃ H ₇ C ₆ H ₃ — (carvaacryl)	H	180-190/15 mm. 132-134/1.1 mm.	153 (HCl)
44 (F 1699)*	Carvaacryl	C ₂ H ₅	167/15 mm.	107 (HCl)
45.....	Carvaacryl	C ₄ H ₉	135-140/1.1 mm.	
46.....	<i>p</i> -C ₆ H ₅ C ₆ H ₄ —	H	190/1.0 mm.	139 (HCl)

TABLE 23—Concluded

NO.	R	R'	BOILING POINT °C.	MELTING POINT OF SALT °C.
47.....	<i>o</i> -C ₆ H ₅ C ₆ H ₄ —	H	152–155/0.84 mm.	125 (HCl)
48.....	<i>p</i> -CH ₃ OC ₆ H ₄ —	H	186–187/18 mm.	129 (HCl)
49.....	<i>p</i> -CH ₃ OC ₆ H ₄ —	C ₂ H ₅	189–190/24 mm.	128 (HCl)
50.....	<i>m</i> -CH ₃ OC ₆ H ₄ —	H	198/27 mm.	119 (HCl)
51.....	2-C ₁₀ H ₇ —	H	165–167/0.7 mm.	143 (HCl)
52.....	C ₆ H ₅ —	—CH ₂ CH ₂ N(C ₂ H ₅) ₂	151/1.2 mm.	210 (2HCl)
53.....	Carvacyrl	—CH ₂ CH ₂ N(C ₂ H ₅) ₂	150–155/1.1 mm.	173 (2HCl)
54.....	<i>p</i> -HOC ₆ H ₄ —	H	200/30 mm.	179 (picrate) Dihydrochloride hygroscopic
55.....	<i>p</i> -HOC ₆ H ₄ —	C ₂ H ₅		Dihydrochloride hygroscopic
56.....	<i>m</i> -HOC ₆ H ₄ —	C ₂ H ₅	205/30 mm.	Dihydrochloride hygroscopic



NO.	R	R'	BOILING POINT °C.
57.....	C ₆ H ₅ —	H	149/14 mm.
58.....	<i>p</i> -CH ₃ OC ₆ H ₄ —	H	184/18 mm.
59.....	<i>m</i> -CH ₃ OC ₆ H ₄ —	H	188/16 mm.
60.....	<i>p</i> -HOC ₆ H ₄ —	H	192–194/14 mm.
61.....	<i>m</i> -HOC ₆ H ₄ —	H	195/17 mm.

NO.	FORMULA	BOILING POINT °C.
62.....	C ₆ H ₅ NHCH ₂ CH ₂ NHCH ₃	143–145/18 mm.

* Fourneau code number.

TABLE 24
Rhône-Poulenc isocyclic amines (200, 443)

$\text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{NR}'_2$					
RHÔNE-POULENC CODE NUMBER	R	R'	RHÔNE-POULENC CODE NUMBER	R	R'
RP 2236.....	H	CH ₃	RP 2347...	<i>i</i> -C ₃ H ₇	CH ₃
RP 2315 (F 1571)*.....	C ₂ H ₅	C ₂ H ₅	RP 2349....	CH ₂ =CHCH ₂ —	CH ₃
RP 2323.....	C ₆ H ₅ CH ₂ —	C ₂ H ₅	RP 2352....	C ₆ H ₅ CH ₂ CH ₂ —	CH ₃
RP 2325.....	C ₂ H ₅	CH ₃	RP 2354....	<i>p</i> -CH ₃ OC ₆ H ₄ CH ₂ —	CH ₃
RP 2337.....	CH ₃	CH ₃	RP 2355....	<i>p</i> -C ₆ H ₅ OC ₆ H ₄ CH ₂ —	CH ₃
RP 2338.....	<i>n</i> -C ₄ H ₉	CH ₃	RP 2357....	C ₂ H ₅	CH ₃
RP 2339 (Antergan).....	C ₆ H ₅ CH ₂ —	CH ₃	RP 2358....	C ₂ H ₅	C ₄ H ₉
RP 2342.....	<i>n</i> -C ₃ H ₇	CH ₃			
RHÔNE-POULENC CODE NUMBER		FORMULA			
RP 2360.....		$\text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$			
		CH ₂ C ₆ H ₅			
RP 2368.....		$\text{C}_6\text{H}_5\text{N}[\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2]_2$			
RP 2378.....		$\text{p-H}_2\text{NC}_6\text{H}_4\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$			
		CH ₂ C ₆ H ₅			
RP 2488.....		$\text{C}_6\text{H}_5\text{NCH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{N}(\text{CH}_3)_2$			
		C ₄ H ₉			
RP 2497.....					
RP 2501.....		$\text{C}_6\text{H}_5\text{CH}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$			
		CH ₂ C ₆ H ₅			
RP 2504.....		$\text{C}_6\text{H}_5\text{NCH}(\text{CH}_3)\text{CH}_2\text{N}(\text{CH}_3)_2$			
		C ₂ H ₅			
RP 2511.....		$\text{C}_6\text{H}_5\text{NCH}(\text{CH}_3)\text{CH}_2\text{N}(\text{CH}_3)_2$			
		C ₄ H ₉			
RP 2565.....		(C ₆ H ₅) ₂ NCH ₂ CH ₂ N(CH ₃) ₂			

* Fourneau code number.

TABLE 24—Continued

RHÔNE-POULENC CODE NUMBER	FORMULA
RP 2612.....	$\begin{array}{c} \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \\ \\ \text{C}_6\text{H}_{13}(n) \end{array}$
RP 2614.....	$\begin{array}{c} \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \\ \\ \text{C}_7\text{H}_{15}(n) \end{array}$
RP 2621.....	$\begin{array}{c} \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \\ \\ \text{CH}_2\text{CH}=\text{CHC}_6\text{H}_5 \end{array}$
RP 2630.....	$\begin{array}{c} \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \\ \\ \text{CH}_2\text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5 \end{array}$
RP 2637.....	$\begin{array}{c} \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \\ \\ \text{CH}_2\text{C}_6\text{H}_4\text{OH}-p \end{array}$
RP 2639.....	$\begin{array}{c} p\text{-CH}_3\text{C}_6\text{H}_4\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \\ \\ \text{CH}_2\text{C}_6\text{H}_5 \end{array}$
RP 2665.....	$\begin{array}{c} \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \\ \\ \text{C}_2\text{H}_6 \end{array}$
RP 2650.....	$\begin{array}{c} \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{NH}_2 \\ \\ \text{C}_2\text{H}_6 \end{array}$
RP 2744.....	$\begin{array}{c} \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \\ \\ \text{H} \end{array}$
RP 2757.....	$\begin{array}{c} \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \\ \\ \text{C}_6\text{H}_{11} \end{array}$
RP 2762.....	$\begin{array}{c} \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2^+ \text{I}^- \\ \\ \text{CH}_2\text{C}_6\text{H}_5 \end{array}$
RP 2768.....	$\begin{array}{c} \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \\ \\ \text{CH}_2\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2-p \end{array}$

TABLE 24—*Concluded*

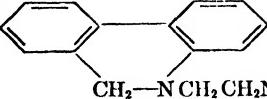
RHÔNE-POULENC CODE NUMBER	FORMULA
RP 2776.....	$\text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ $\text{CH}_2\text{COCH}_2\text{SCH}=\text{NH}$
RP 2813.....	$\text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ COC_6H_5
RP 2835.....	$\text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ $\text{CH}_2\text{C}_6\text{H}_5$ ↓ O
RP 2846.....	$\text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ $\text{CH}_2\text{COOC}_2\text{H}_5$
RP 2855.....	$\text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ $\text{CH}_2\text{CHI}(\text{OC}_2\text{H}_5)_2$
RP 2881.....	$\text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ $\text{CH}_2\text{CH}_2\text{OII}$
RP 2886.....	$\text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ CH_2CONH_2
RP 2887.....	$\text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ $\text{CH}_2\text{CH}_2\text{OCH}_3$
RP 2889.....	$\text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ C_6H_5 $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$
RP 2902.....	$\text{C}_2\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$  $\text{C}_2\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$
RP 3110.....	

TABLE 24A
Antihistamine activity of aniline derivatives (443)

NO.	R	ANTIHISTAMINE ACTIVITY	
		Aerosol*	Ileal spasm†
$\begin{array}{c} \text{C}_6\text{H}_5\text{NCH}_2\text{CH}_2\text{R} \\ \\ \text{C}_2\text{H}_5 \end{array}$			
1	—NH ₂	Inactive	0
2 (RP 2325)	—N(CH ₃) ₂	5	1/15
3 (F 1571)	—N(C ₂ H ₅) ₂	10	1/100
4	—N(C ₄ H ₉) ₂	200	Inactive
$\begin{array}{c} \text{C}_6\text{H}_5\text{N R} \\ \\ \text{C}_2\text{H}_5 \end{array}$			
5	—CH ₂ CH ₂ CH ₂ N(CH ₃) ₂	1.5	1/50
6	—CH ₂ CH(CH ₃)N(CH ₃) ₂	100	
7	—CH ₂ CH ₂ CH ₂ CH ₂ N(CH ₃) ₂	Inactive	
$\begin{array}{c} \text{C}_6\text{H}_5\text{N CH}_2\text{C}_6\text{H}_5 \\ \\ \text{CH}_2\text{CH}_2\text{R} \end{array}$			
8 (Antergan)	—N(CH ₃) ₂	1	1
9	—N(C ₂ H ₅) ₂	20	1/6
10	—N(CH ₃)OH ⁺	10	
11	—N(CH ₃) ₂	10	1/50
	↓ O		
$\begin{array}{c} \text{C}_6\text{H}_5\text{N CH}_2\text{C}_6\text{H}_5 \\ \\ \text{R} \end{array}$			
12	—CH ₂ CH ₂ CH ₂ N(CH ₃) ₂	20	1/15
13	—CH ₂ CH(CH ₃)N(CH ₃) ₂	25	
$\begin{array}{c} \text{C}_6\text{H}_5\text{N CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \\ \\ \text{R} \end{array}$			
14	H	Inactive	1/100
15	CH ₃	50	1/100
16	n-C ₂ H ₇	2.5	1/8
17	n-C ₄ H ₉	2.5	1/4
18	n-C ₆ H ₁₁	2.5	

TABLE 24A—Concluded

NO.	R	ANTIHISTAMINE ACTIVITY	
		Aerosol*	Ileal spasm†
19	<i>n</i> -C ₆ H ₁₃	8	1/10
20	<i>n</i> -C ₇ H ₁₅	50	1/30
21	<i>i</i> -C ₃ H ₇	20	1/50
22	—CH ₂ CH=CH ₂	15	1/15
23	Cyclo-C ₆ H ₁₁	Inactive	1/100
24	—CH ₂ CH ₂ OH	Inactive	
25	—CH ₂ CH ₂ OCH ₃	2.5	1/4
26	—CH ₂ CH ₂ OC ₂ H ₅	2	1
27	—CH ₂ CH ₂ COOC ₂ H ₅	20	
28	—CH ₂ COSCH=CH ₂	1.2	1/1.2
29	—COC ₆ H ₅	10	
30	—CH ₂ CH ₂ N(CH ₃) ₂	0	0
31	—C ₆ H ₅	50	
32	—CH ₂ CH=CHC ₆ H ₅	20	

* Dose of antihistamine in milligrams to prevent bronchospasm by inhalation of an aerosol or histamine.

† Antihistamine activity on isolated guinea-pig intestine. Antergan = 1.

TABLE 25
Isocyclic alkylenediamines

NO.	R	R'	RNCH ₂ CH ₂ N(CH ₃) ₂	BOILING POINT	MELTING POINT OF SALT	REFERENCES
1 (RP 2339).....	C ₆ H ₅ —	C ₆ H ₅ CH ₂ —		157-158/1 mm. 195-196/0.03 mm.	208 (HCl) 202 (HCl) 178 (2HCl)	(64) (228, 396) (200)
2 (RP 2503).....	C ₆ H ₅ CH ₂ —	C ₆ H ₅ CH ₂ —			158 (CH ₃ I) 131 (CH ₃ Br)	(211) (211)
3 (RP 2565).....	C ₆ H ₅ —	C ₆ H ₅ —		160-175/6 mm.	262 (HCl)	(65)
4 (RP 2349).....	C ₆ H ₅ —	CH ₂ =CHCH ₂ —		138-141/11 mm.	254 (HCl)	(65)
5.....	o-CH ₃ OC ₆ H ₄ —	C ₆ H ₅ CH ₂ —		200-206/11 mm.	161 (HCl)	(52, 146)
6 (RP 2352).....	C ₆ H ₅ —	C ₆ H ₅ CH ₂ CH ₂ —		210-211/12 mm.		(228, 396)
7 (RP 2354).....	C ₆ H ₅ —	p-CH ₃ OCH ₂ CH ₂ —		225-227/12 mm.	184 (CH ₃ I)	(228, 396) (211)
8 (RP 2639).....	o-CH ₃ C ₆ H ₄ —	C ₆ H ₅ CH ₂ —		181-184/11 mm.		(228, 396)
9.....	p-CH ₃ OCH ₂ CH ₂ —	C ₆ H ₅ CH ₂ —		219-221/12 mm. 167-169/0.6 mm.	182 (HCl)	(228, 396) (230)

10.....	2,5-(CH ₂ O) ₂ C ₄ H ₉ —	C ₄ H ₉ CH ₂ —	141-143/0.1 mm.	(228, 396)
11.....	o-C ₂ H ₅ OC ₄ H ₉ —	C ₆ H ₅ CH ₂ —	200-203/10 mm.	(228, 396)
12.....	C ₆ H ₅ —	m-CH ₃ OC ₆ H ₄ —	217-218/12 mm.	(228, 396)
13.....	o-O ₂ NC ₆ H ₄ —	H	129-135/2 mm.	(415)

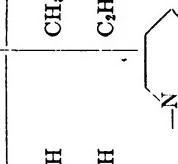
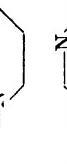


14.....	o-CH ₃ OC ₆ H ₄ —	H	153 (HCl)	(396)
15.....	o-CH ₃ OC ₆ H ₄ —	C ₄ H ₉ CH ₂ —	210/11 mm.	(396)
16 (RP 2360).....	C ₆ H ₅ —	C ₆ H ₅ CH ₂ —	170-175/2 mm.	(64, 200)



NO.	R	R'	n	BOILING POINT °C.	MELTING POINT OF HYDROCHLORIDE °C.	REFERENCES
17 (F 1167).....	C ₆ H ₅ —	H	3	218-219/10 mm.	123	(396)
18.....	C ₆ H ₅ CH ₂ —	H	3	149-150/11 mm.	137	(396)
19 (F 1571) (RP 2315).....	C ₆ H ₅ —	C ₂ H ₅	2	209-210/11 mm.	170	(396)
20 (RP 2323).....	C ₆ H ₅ —	C ₆ H ₅ CH ₂ —	2			(228, 396)

TABLE 25—Continued

NO.	R	R'	R"	n	BOILING POINT		MELTING POINT OF SALT OR BASE °C.	REFERENCES
					°C.	mm.		
21.....	C ₆ H ₅ CH ₂ —	H	CH ₃	2	210–212/13	mm.	175 (HCl)	(228, 396)
22.....	C ₆ H ₅ CH ₂ —	H	C ₂ H ₅	2	206–208/14	mm.	194 (HCl)	(396)
23.....	C ₆ H ₅ CH ₂ —			2	201–205/0.1	mm.	206 (HCl)	(323, 396)
24.....	m-CH ₃ OCH ₂ CH ₂ —			2	215–218/0.8	mm.		(228, 396)
25.....	H			1			190 (HCl)	(396)
26.....	C ₆ H ₅ CH ₂ —			1	143 (base)		143 (base)	(396)
							214 (HCl)	



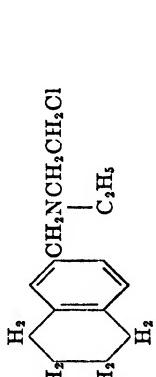
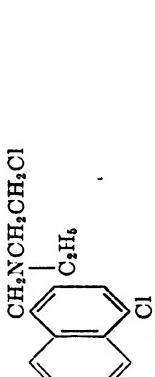
NO.	R	R	BOILING POINT °C.	MELTING POINT OF SALT °C.	REFERENCES
27	-CH ₂ CH ₂ N(C ₆ H ₅) ₂	173-174/2 mm.	170 (HCl)	(64)
28	-CH ₂ CH ₂ N ⁺ (CH ₃) ₂ [Br ^{-]}	183 (HCl)	183 (HCl)	(65)
29 (RP 2762)	-CH ₂ CH ₂ N ⁺ (CH ₃) ₃ [I ^{-]}	169-171/2-3 mm.	152 (HCl)	(65)
30	Isoamyl	169-171/2-3 mm.	183 (HCl)	(65)
31	-CH ₂ CH ₂ CH ₂ N(CH ₃) ₂	(208)
32	-CH ₂ CH(CH ₃)N(CH ₃) ₂	(209)
33	-CH ₂ CH(CH ₃)N(CH ₃) ₂	(209)

N-(2-Haloalkyl)-1-naphthalenemethylamine derivatives (265)



NO.	R	X	ANTIHISTAMINE ACTIVITY*	NO.	R	X	ANTIHISTAMINE ACTIVITY*
34	CH ₃	Cl	0.05 mg./kg.	4 [†]	sec-C ₄ H ₉	Cl	12.5 mg./kg.
35	C ₆ H ₅	Cl	0.025 mg./kg.	42	i-C ₄ H ₉	Cl	>12.5 mg./kg.
36	C ₆ H ₅	Br (HBr)	0.03 mg./kg.	43	n-C ₆ H ₁₁	Cl	>12.5 mg./kg.
37	n-C ₃ H ₇	Cl	1.0 mg./kg.	44	n-C ₆ H ₁₃	Cl	>25.0 mg./kg.
38	i-C ₃ H ₇	Cl	<3.0 mg./kg.	45	-CH ₂ CH ₂ OCH ₂ H ₅	Cl	1.5 mg./kg.
39	Amyl	Cl	3.0 mg./kg.	46	-CH ₂ CH ₂ Cl	Cl	25.0 mg./kg.
40	n-C ₄ H ₉	Cl	12.5 mg./kg.	47	C ₂ H ₅	OH	>25.0 mg./kg.

TABLE 25—*Concluded.*
N-(Haloalkyl)naphthalenealkylamines

NO.	FORMULA	ANTIHISTAMINE ACTIVITY*	REFERRENCES	
			mg./kg.	
48.....				
49.....				
50.....		>12.5		
Miscellaneous diamines†				
NO.	FORMULA	BOILING POINT °C.	MELTING POINT OF SALT °C.	REFERRENCES
51.....				(323)
52.....				(323)

53.....	 $\text{CH}_2\text{CH}(\text{CH}_3)\text{NHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	142-145/5 mm.	208 (HCl) 196 (picrate)	(307)
54.....	 $\text{CH}_2\text{CH}(\text{CH}_3)\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ $\quad \quad \quad \quad $ $\quad \quad \quad \quad \text{CHO}$	193-195/5 mm.		(307)
55.....	 $\text{C}_2\text{H}_5\text{NCH}_2\text{CH}_2\text{NH}_2$ $\quad \quad \quad \quad $ $\quad \quad \quad \quad \text{CH}_2\text{C}_6\text{H}_5$	206-208/14 mm.	194 (HCl)	(288)
56.....	 $\text{C}_2\text{H}_5\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ $\quad \quad \quad \quad $ $\quad \quad \quad \quad \text{CH}_2\text{C}_6\text{H}_5$	218-219/10 mm.	132 (HCl)	(288)
57.....	 $\text{C}_2\text{H}_5\text{NCH}_2\text{CH}(\text{OCH}_3)\text{CH}_2\text{N}(\text{CH}_3)_2$ $\quad \quad \quad \quad $ $\quad \quad \quad \quad \text{CH}_2\text{C}_6\text{H}_5$	203-210/11 mm.	152 (HCl)	(288)
58.....	 $\text{C}_2\text{H}_5\text{NCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	149-150/11 mm.		(288)

* Minimum effective dose (subcutaneous) for diminution of histamine-induced bronchospasm in guinea pigs.

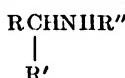
† Added after the table had been assembled.

TABLE 26
Benzhydrylamines tested by Loew, Kaiser, and Moore (263)
 $(C_6H_5)_2CHNHR$

NO.	R	ANTIHISTAMINE ACTIVITY*
1.....	$-CH_2CH_2N$	<2
2.....	$-CH_2CH_2N(C_2H_5)_2$	<2
3.....	$-CH_2CH_2CH_2N(C_2H_5)_2$	<1
4.....	$-CH_2CH_2NHC_2H_5$	<1
	NAME	
5.....	Benadryl	33

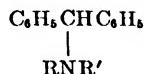
* Efficacy in the prevention of fatal histamine-induced bronchoconstriction in guinea pigs.

TABLE 27
C-Substituted benzhydrylamines (4)



NO.	R	R'	R''
1.....	C_6H_5-	C_6H_5-	H
2.....	C_6H_5-	C_6H_5-	C_6H_{13}
3.....	$p-CH_3C_6H_4-$	C_6H_5-	H
4.....	$p-CH_3C_6H_4-$	$p-CH_3C_6H_4-$	H
5.....	$p-CH_3OC_6H_4-$	C_6H_5-	H
6.....	$p-CH_3OC_6H_4-$	C_6H_5-	$-CH_2CH_2N(C_2H_5)_2$
7.....	$p-CH_3OC_6H_4-$	C_6H_5-	$-COCH_2CH_2COOH$
8.....	$2,4-(CH_3O)_2C_6H_3-$	C_6H_5-	H
9.....	$2,5-(CH_3O)_2C_6H_3-$	C_6H_5-	H
10.....	$3,4-(CH_3O)_2C_6H_3-$	C_6H_5-	H
11.....	$p-ClC_6H_4-$	C_6H_5-	H
12.....	$p-ClC_6H_4-$	$p-ClC_6H_4-$	H
13.....	$p-HOOCC_6H_4-$	C_6H_5-	H
14.....	$p-CH_3OC_6H_4-$	C_6H_5-	$-CH_2CH_2OCH_3$
15.....	$p-CH_3OC_6H_4-$	$p-CH_3OC_6H_4-$	$-CH_2CH_2N(C_2H_5)_2$
16.....	$p-C_6H_5OC_6H_4-$	C_6H_5-	H
17.....	$p-C_6H_5OC_6H_4-$	$p-CH_3OC_6H_4-$	H

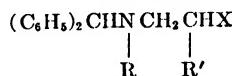
TABLE 28
N-Substituted benzhydrylamines (98)



NO.	R	R'	MELT- ING POINT	MELTING POINT OF SALT		YIELD per cent
				°C.	°C.	
1	CH ₃	p-CH ₃ OC ₆ H ₄ CH ₂ -	62		150 (HCl)	83
2	CH ₃	-CH ₂ CH ₂ OH			179 (HCl)	62
3	C ₆ H ₅ CH ₂ -	-CH ₂ CH ₂ OH			191 (HCl)	75
4	CH ₃	-CH ₂ CH ₂ Cl			171 (HCl)	90
5	C ₆ H ₅ CH ₂ -	-CH ₂ CH ₂ Cl			227 (2HCl)	63
6	CH ₃	-CH ₂ CH ₂ N(CH ₃) ₂				67
7	CH ₃	-CH ₂ CH ₂ N 		237 (2HCl)		70
8*	C ₆ H ₅ CH ₂ -	-CH ₂ CH ₂ N(CH ₃) ₂			102 (maleate)	

* Reference 70.

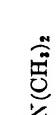
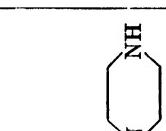
TABLE 29
Benzhydryl-2-haloalkylamines (259, 363)



NO.	R	R'	X	MELTING POINT OF HYDROCHLORIDE		ANTIHISTAMINE ACTIVITY*
				°C.	mg./kg.	
1	CH ₃	H	Cl	192	12.5	
2	C ₂ H ₅	H	Cl	169	12.5	
3	C ₂ H ₅	H	Br			
4	C ₃ H ₇	H	Cl		25.0	
5	i-C ₄ H ₉	H	Cl		25.0	
6	Allyl	H	Cl			
7	C ₆ H ₁₃	H	Cl			
8	n-C ₆ H ₁₃	H	Cl			
9	sec-C ₄ H ₉	H	Cl		12.5	
10	CH ₃	CH ₃	Br			
11	C ₂ H ₅	CH ₃	Cl			
12	Allyl	CH ₃	Cl			
13	C ₆ H ₅	CH ₃	Cl			

* Dose in milligrams per kilogram which failed to diminish histamine-induced bronchospasm in guinea pigs (subcutaneous).

TABLE 30
N-Isocyclic-substituted heterocycles prepared by Cerkonikov and coworkers (73, 74, 75)

No.	R	R'	BOILING POINT	MELTING POINT	YIELD	L.D. ₁₀₀	ANTIHISTAMINE ACTIVITY*
						per cent	
						mg.	
1....	C ₄ H ₉ —	p-(C ₂ H ₅) ₂ NC ₆ H ₄ —		136 234 (3HCl) 185 d. (tripicrate)	48.9	70	>50
2....	C ₄ H ₉ —	p-CH ₃ OCH ₂ H ₄ —	192-194/0.4 mm.	165 216 (2HCl)	47.3	30	25-50
3....	C ₄ H ₉ —	p-HOC ₂ H ₅ —		283 d. (2HBr)	100	25	>25
4....	C ₄ H ₉ —	—CH ₂ CH ₂ OH	172-175/0.5 mm.	83 187 (2HCl)	43.4	30	25-50
5....	C ₄ H ₉ —	C ₆ H ₅ COOCH ₂ CH ₂ —		214 (HCl) 197 (2HCl)	100	60	25-50
6....	C ₄ H ₉ —	—CH ₂ CH ₂ N(CH ₃) ₂	228-230/0.5 mm.	267 (2HCl) 196 d. (dipicrate)	51.8	15	12.5
7....	C ₄ H ₉ —	—CH ₂ CH ₂ N 	195-200/0.6 mm.	283 (3HCl) 169 d. (tripicrate)	31.2	20	>25
8....	C ₄ H ₉ —	—CH ₂ CH ₂ N 		173 269 (4HCl) 213 (tetrapirocate)	61.9	10	>25

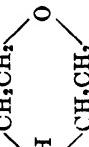
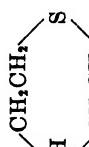
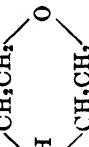
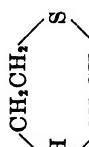
9....	C ₄ H ₆ —		228-230/0.4 mm. 246 (HCl) 269 (2HBr) 203 (picrate)	122 246 (HCl) 269 (2HBr) 203 (picrate)	15	20-40
10....	C ₄ H ₆ —		220-230/0.5 mm.	231 (2HCl) 189 (picrate)	21.3	
11....	C ₄ H ₆ —		175-180	267 (3HCl) 204 d. (picrate)	52.5	>25
12....	p-HOC ₄ H ₃ —		198-200/0.2 mm.	220 (2HCl) 205 (picrate)	30	>100
13....	p-CH ₃ OCH ₂ H ₂ —		H		1.5	>20
14....	p-CH ₃ C ₆ H ₄ —		H		1.5	>20
15....	1-C ₁₀ H ₇ —		H		1.0	>20
16....	C ₄ H ₆ —		-COCH ₃		4	>20
17....	C ₄ H ₆ —		C ₄ H ₆ CH ₂ —		25	>40
18....	C ₄ H ₆ —		-CH ₂ CH ₂ N(C ₂ H ₅) ₂	235-236/0.4 mm. 185 (2HCl) 183 (picrate)	36.4	>50
19....	C ₄ H ₆ CH ₂ —		-CH ₂ CH ₂ N(CH ₃) ₂	190-210/0.4 mm. 237 (2HCl) 223 (picrate)	56.4	70

TABLE 30—Continued

No.	R	R'	BOILING POINT	MELTING POINT	YIELD	ANTIHISTAMINE ACTIVITY*	
						per cent	mg.
RN NR'—Continued							
20....	C ₄ H ₉ —			193	39.6	30	>50
	CH ₂ CH ₂	CH—		270 (3HCl) 206 (dipicrate)			
		CH ₂ CH ₂					
21....				175			
				226 (picrate)			
22....	C ₄ H ₉ —			180	63	20	25
23....	C ₄ H ₉ —	[-CH ₂ CH ₂ CH ₂ N(CH ₃) ₂]		241 (4HCl) 197 (tetrapicrate)	59	4	15
RN R'							
24....	C ₄ H ₉ —	—N(CH ₃) ₂	123-126/0.5 mm.	48	6	30	
				253 (2HCl) 204 (dipicrate)			
25....	CH ₃		174-175				
				312 (2HCl)	31.6	45	>50
26....	C ₄ H ₉ —	—CH ₂ N(CH ₃) ₂	200-202/20 mm.	125 (picrate) 164 (picrolonate)	45.3	0.75	>2
27....		H	192-194	289 (2HCl)	33.3	25	100

	<i>F₁</i> , MCIA					
28....		93-94/20 mm.	278 (2HCl) 219 (dipicrate) 234 (dipicolonate)	61	25	>50
29....		265-267	245 (HBr) 192 d. (tetrapicrate)	25.5	2.5	15

* Lethal dose in milligrams to kill mice (mode of administration not stated in *Chemical Abstracts*).

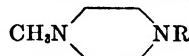
† Milligrams necessary to protect guinea pigs against one lethal dose of histamine.

TABLE 31
Dibenzylpiperazines (243, 284)



NO.	R, R'	MELTING POINT	MELTING POINT OF HYDROCHLORIDE
		°C.	°C.
1.....	H	92	240 d.
2.....	NO ₂		
3.....	NH ₂		
4.....	OH		

TABLE 32
Unsymmetrically disubstituted piperazines (5, 15)



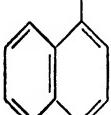
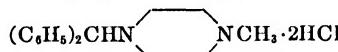
NO.	R	MELTING POINT OF HYDROCHLORIDE OR BASE	YIELD
		°C.	per cent
1.....	<i>o</i> -O ₂ NC ₆ H ₄ —	235 (HCl)	60
2.....	<i>p</i> -O ₂ NC ₆ H ₄ —	270 (HCl)	90
3.....	<i>p</i> -H ₂ NC ₆ H ₄ —	274 (HCl)	61
4.....	2,4-(O ₂ N) ₂ C ₆ H ₃ —	234 (HCl)	100
5.....	CH ₂ — 	245 (2HCl)	20
6.....	CH ₂ — 	213 (2HCl)	90
7.....	CH ₂ — 	220 (2HCl)	65

TABLE 32—Concluded

NO.	R	MELTING POINT OF HYDROCHLORIDE OR BASE		YIELD <i>per cent</i>
		°C.	2HCl)	
8.....	$p\text{-C}_6\text{H}_5\text{C}_6\text{H}_4\text{CH}-$ C_6H_5	220	(2HCl)	85
9.....	$p\text{-C}_6\text{H}_5\text{OC}_6\text{H}_4\text{CH}-$ C_6H_5	204 (2HCl) 91 (base)		65
10.....	$\text{C}_6\text{H}_5\text{COCH}-$ C_6H_5	228 (2HCl)		90
11.....	$\text{C}_6\text{H}_5\text{CHOHCl}-$ C_6H_5	234 (2HCl)		60
12.....	$p\text{-HOC}_6\text{H}_4\text{COCH}-$ C_6H_5	216 d. (2HCl)		65
13.....	$\text{C}_6\text{H}_5\text{CH}_2-$	250 d. (2HCl)		
FORMULA				
14.....	$\text{C}_6\text{H}_5\text{CH}_2\text{N} \begin{array}{c} \text{---} \\ \\ \text{C}_6\text{H}_4 \end{array} \text{NC}_2\text{H}_5$	250 d. (2HCl)		

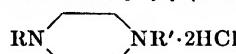
TABLE 33
N-Benzhydryl-N'-methylpiperazines (16)

NO.	BENZHYDRYL SUBSTITUTION	BOILING POINT	MELTING POINT OF SALT OR BASE	
			°C.	2HCl)
1.....	None		>255	d. (2HCl)
2.....	Methochloride hydrochloride		240	d. (2HCl)
3.....	1,2,3,4,5,6-Hexahydro		249	d. (2HCl)
4.....	2-Cl		248	(2HCl)
5.....	3-Cl		252	(2HCl)
6.....	4-Cl	137-145/0.12 mm.	216.5	(2HCl)
7.....	2-Br		252	d. (2HCl)
8.....	4-Br		78	(base)
9.....	4-Cl ₂ -4'-Cl		228	(2HCl)
10.....	2,4-Cl ₂		226	(2HCl)
11.....	3,4-Cl ₂		233	(2HCl)
			238	(2HCl)

TABLE 33—*Concluded*

NO.	BENZHYDROXYL SUBSTITUTION	BOILING POINT	MELTING POINT OF SALT OR BASE
12.....	4,4'-Cl ₂		°C.
13.....	4-Cl-4'-Br		249 (2HCl) 78 (base)
14.....	2,4,4'-Cl ₃		243 (2HCl) 101 (base)
15.....	2-OCH ₃		258 (HCl)
16.....	3-OC ₂ H ₅	140-150/0.04 mm.	196 d. (2HCl) 228 (2HCl) 77 (base)
17.....	4-OCH ₃		192 (2HCl)
18.....	4'-OCH ₃ -1,2,3,4,5,6-hexa-hydro		218 d. (2HCl)
19.....	2-OCH ₃ -5-Cl		227 (2HCl) 125 (base)
20.....	4-OCH ₃ -3-Cl		221 d. (2HCl)
21.....	4-OCH ₃ -4'-Cl		184 d. (2HCl) 65 (base)
22.....	4-OCH ₃ -3-Br		209 (2HCl)
23.....	4-OCH ₃ -2'-Br		213 d. (2HCl)
24.....	4-OCH ₃ -2,4'-Cl ₂	140*/0.0002-0.0003 mm.	172 (2HCl)
25.....	4-OCH ₃ -3,4'-Cl ₂	140*/0.0002-0.0003 mm.	211 (2HCl)
26.....	4,4'-(OCH ₃) ₂ -3,3'-Cl ₂		227 (2HCl) 99 (base)

* Bath temperature.

TABLE 34
*Antihistaminic activity of piperazines** (68)

COMPOUND NO.	R	R'	ANTIHISTAMINE ACTIVITY†
46-125.....	C ₆ H ₅ CH ₂ —	CH ₃	Slight
46-126.....	C ₆ H ₅ CH ₂ —	—CH ₂ CH ₃	Very slight
895.....	C ₆ H ₅ CH ₂ —	n-Lauryl	None
47-83.....	(C ₆ H ₅) ₂ CH—	CH ₃	100 per cent
47-282.....	p-ClC ₆ H ₄ CH— C ₆ H ₅	CH ₃	400 per cent

* Compounds prepared at the laboratories of Burroughs Wellcome and Company.

† Antihistamine potency in terms of Benadryl=100 per cent.

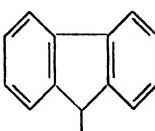
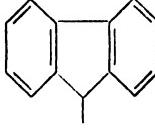
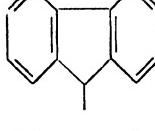
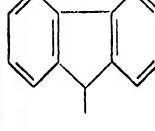
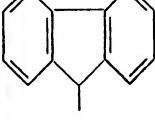
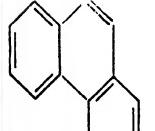
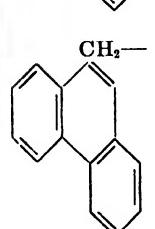
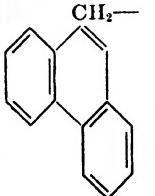
TABLE 35
*Isocyclic-substituted piperazines (183, 184)**

NO.	R	R'	R''	BOILING POINT	MELTING POINT OF SALT OR BASE
1.	C ₆ H ₅ —	C ₆ H ₅ —	CH ₃		°C.
2...	C ₆ H ₅ —	C ₆ H ₅ —	—CH ₂ OH	260 (2HCl)	108 (base)
3...	C ₆ H ₅ —	C ₆ H ₅ —	C ₂ H ₅	190 (2HCl)	242 (2HCl)
4...	C ₆ H ₅ —	C ₆ H ₅ —	—CH ₂ CH ₂ OH	229 d.	229 d. (2HCl)
5...	C ₆ H ₅ —	C ₆ H ₅ —	n-C ₄ H ₉	248 d.	248 d. (2HCl)
6...	C ₆ H ₅ —	C ₆ H ₅ —		295 (0.5-H2SO4)	295 (0.5-H2SO4)
7...	C ₆ H ₅ —	C ₆ H ₅ —	—CH ₂ CH ₂ N(CH ₃) ₂	162-164/0.7 mm.	257 (2HCl)
8...	C ₆ H ₅ —	p-FC ₆ H ₄ —	CH ₃	140-141/0.6 mm.	231 (HCl) 64 (base)
9...	C ₆ H ₅ —	p-ClC ₆ H ₄ —	CH ₃	160-161/0.5 mm.	224 (HCl)
10...	C ₆ H ₅ —	p-BrC ₆ H ₄ —	CH ₃	175-176/0.8 mm.	250 (HCl)
11...	C ₆ H ₅ —	p-IC ₆ H ₄ —	CH ₃	180-181/0.5 mm.	261 (HCl)
12...	C ₆ H ₅ —	o-ClC ₆ H ₄ —	CH ₃	179-180/2 mm.	273 (HCl)
13...	C ₆ H ₅ —	m-ClC ₆ H ₄ —	CH ₃	177/1.5 mm.	250 (HCl)
14...	C ₆ H ₅ —	p-CH ₃ C ₆ H ₄ —	CH ₃	159-160/1 mm.	229 (HCl)
15...	C ₆ H ₅ —	p-CH ₃ OC ₆ H ₄ —	CH ₃	168-169/0.7 mm.	195 (2HCl)
16...	Cyclo-C ₆ H ₁₁	p-ClC ₆ H ₄ —	CH ₃		279 d. (2HCl)
17...	n-C ₃ H ₇	p-ClC ₆ H ₄ —	CH ₃	142-143/1.7 mm.	177 (2HCl)
18...	p-ClC ₆ H ₄ —	p-ClC ₆ H ₄ —	CH ₃	168/0.3 mm.	246 (2HCl)
19...	C ₆ H ₅	p-ClC ₆ H ₄ —	C ₂ H ₅		228 (2HCl)
20...	C ₆ H ₅ —	p-ClC ₆ H ₄ —	n-C ₄ H ₉		255 (2HBr)
21...	C ₆ H ₅ —	p-ClC ₆ H ₄ —	—CH ₂ CH ₂ CH ₂ - CH ₂ OH		212 (2HCl)
22...	C ₆ H ₅ —	p-ClC ₆ H ₄ —	n-C ₁₀ H ₂₁	245-250/0.4 mm.	

TABLE 35—Continued

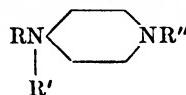
NO.	R	R'	YIELD	BOILING POINT		MELTING POINT OF SALT OR BASE
				°C.		
23.....	$p\text{-BrC}_6\text{H}_4\text{CH}_2\text{--}$	CH ₃	86			294 (2HCl)
24.....	(C ₆ H ₅) ₂ CHCH ₂ —	CH ₃	40			279 (2HCl)
25.....	(C ₆ H ₅) ₂ C=CHCH ₂ —	CH ₃	71	165–170/0.9 mm.		140 (HCl)
26.....		H	37	155–156/1 mm.		228 (HCl)
27.....		CH ₃	100			241 (2HCl)
28.....		—CH ₂ CH ₂ OH	81			206 d. (2HCl)
29.....			27			164 (base)
30.....		H	33	155–160/1 mm.		195 (HCl)
31.....		CH ₃	82			281 d. (2HCl)
32.....		—CH ₂ CH ₂ OH	33			241 d. (2HCl)
33.....			23			160 (base)

TABLE 35—Concluded

NO.	R	R'	YIELD	BOILING POINT °C.	MELTING POINT OF SALT OR BASE °C.
34.....		H	89		285 d. (2HCl)
35.....		CH ₃	57		268 d. (2HBr)
36.....		-CH ₂ CH ₂ OH	68		244 d. (2HCl) 144 (base)
37.....			100		292 d. (base)
38....		CH ₂ —	43		255 d. (2HCl)
39....			100		286 (2HCl) 254 (base)

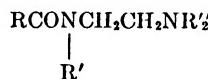
* Compounds prepared at the Abbott Laboratories.

TABLE 36
4-Aminopiperidines (340, 342)



NO.	R	R'	R''	BOILING POINT	MELTING POINT OF SALT OR BASE
1...	H	C ₆ H ₅ CH ₂ —	CH ₃	168–172/17 mm.	227 d. (dipicrate)
2...	H	C ₆ H ₅ CH ₂ —	C ₂ H ₅	113–115/0.2 mm.	304 (2HCl)
3...	H	—CH ₂ CH ₂ OH	C ₂ H ₅	117–119/17 mm.	228 d. (dipicrate)
4...	II	—CH ₂ CH ₂ N(CH ₃) ₂	C ₂ H ₅	136–139/17–18 mm.	219 d. (dipicrate)
5...	C ₆ H ₅ CH ₂ —	—CH ₂ CH ₂ N(CH ₃) ₂	C ₂ H ₅	185–188/0.7 mm.	239 d. (tripicrate)
					100 (base)
					195 d. (tripicrate)

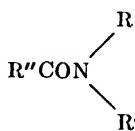
TABLE 37
Amides of ethylenediamine (444)



NO.	R	R'	R''	BOILING POINT	YIELD
1.....	C ₆ H ₅ —	C ₆ H ₅ —	CH ₃	158–159/1 mm.	80
2.....	C ₆ H ₅ —	p-CH ₃ C ₆ H ₄ —	CH ₃	159–162/0.5 mm.	78
3.....	C ₆ H ₅ —	2-C ₆ H ₄ N—	CH ₃	155–158/1 mm.	74
4.....	2-C ₆ H ₄ N—*	H	CH ₃	113–124/1 mm.	29
5.....	2-C ₆ H ₄ N—	C ₆ H ₅ —	CH ₃	177–178/2 mm.	27
6.....	2-C ₆ H ₄ N—	C ₆ H ₅ —	CH ₃	177–178/2 mm.	13
7.....	2-C ₆ H ₄ N—	p-CH ₃ C ₆ H ₄ —	CH ₃	185–190/1 mm.	53
8.....	2-C ₆ H ₄ N—	m-ClC ₆ H ₄ —	CH ₃	182–186/2 mm.	69
9.....	2-C ₆ H ₄ N—	p-ClC ₆ H ₄ —	CH ₃	185–190/1.5 mm.	33
10.....	2-C ₆ H ₄ N—	o-CH ₃ OC ₆ H ₄ —	CH ₃	183–186/1 mm.	28
11.....	2-C ₆ H ₄ N—	C ₆ H ₅ CH ₂ —	CH ₃	196–200/2 mm.	47
12.....	2-C ₆ H ₄ N—	2-C ₆ H ₄ N—	CH ₃	175–179/1 mm.	18
13.....	3-C ₆ H ₄ N—	H	CH ₃	140–143/1 mm.	32
14.....	3-C ₆ H ₄ N—	C ₆ H ₅ —	CH ₃	187–190/1 mm.	51
15.....	3-C ₆ H ₄ N—	C ₆ H ₅ —	C ₂ H ₅	187–189/0.5 mm.	62
16.....	3-C ₆ H ₄ N—	p-CH ₃ C ₆ H ₄ —	CH ₃	180–189/0.5 mm.	64
17.....	3-C ₆ H ₄ N—	m-ClC ₆ H ₄ —	CH ₃	176–185/2 mm.	80
18.....	3-C ₆ H ₄ N—	p-ClC ₆ H ₄ —	CH ₃	185–187/1 mm.	74
19.....	3-C ₆ H ₄ N—	o-CH ₃ OC ₆ H ₄ —	CH ₃	188–192/1 mm.	80
20.....	3-C ₆ H ₄ N—	C ₆ H ₅ CH ₂ —	CH ₃	193–197/2 mm.	
21.....	3-C ₆ H ₄ N—	C ₆ H ₅ CH ₂ —	C ₂ H ₅	193–196/1 mm.	81
22.....	2-C ₆ H ₅ S—†	C ₆ H ₅ CH ₂ —	CH ₃	187–193/0.5 mm.	44
23.....	3-C ₆ H ₄ N—	2-C ₆ H ₂ NS—‡	CH ₃	164–169/0.5 mm.	52

TABLE 37—Concluded

Other amides

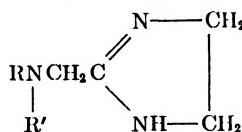


NO.	R	R'	R''	BOILING POINT °C.	MELTING POINT °C.	YIELD per cent
24....	C ₆ H ₅ —	2-C ₆ H ₄ N—	3-C ₆ H ₄ N—		177–178	51
25....	C ₆ H ₅ —	2-C ₆ H ₄ N—	2-C ₆ H ₄ N—		107–108	18
26....	C ₆ H ₅ CH ₂ — 2-C ₆ H ₄ N	H	3-C ₆ H ₄ N—	184–187/0.5 mm.		19
27....	C ₆ H ₅ CH ₂ — 2-C ₆ H ₄ N	H	2-C ₆ H ₄ N—	191–196/2 mm.		32

* Pyridyl.

† Thienyl.

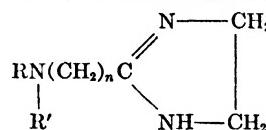
‡ Thiaazyl.

TABLE 38
2-Isocyclic imidazolines

NO.	R	R'	MELTING POINT OF SALT OR BASE	REFERENCES
1....	C ₆ H ₅ —	H	182 (HCl)	(398)
2....	<i>o</i> -CH ₃ OC ₆ H ₄ —	H	200 (HCl) 87 (base)	(399)
3....	<i>p</i> -HOCH ₂ —	H	225 (HCl)	(287)
4....	<i>m</i> -HOCH ₂ —	H	194 (HCl)	(287)
5....	<i>p</i> -CH ₃ OC ₆ H ₄ —	H	181 (HCl) 111 (base)	(287)
6....	<i>p</i> -CH ₃ C ₆ H ₄ —	<i>m</i> -HOCH ₂ —	240 (HCl) 175 (base)	(188, 282, 287)
7....	<i>p</i> -CH ₃ C ₆ H ₄ —	<i>m</i> -CH ₃ OC ₆ H ₄ —	151 (HCl) 93 (base)	(287)
8 (Anti- stine)...	C ₆ H ₅ —	C ₆ H ₅ CH ₂ —	229 (HCl) 121 (base) 159 (picrate)	(82, 83, 86, 207, 285, 396)
9....	<i>p</i> -HOCH ₂ —	C ₆ H ₅ CH ₂ —	229 (HCl)	(84, 207, 396)
10....	<i>p</i> -HOCH ₂ —	C ₆ H ₅ CH ₂ —	228 (HCl)	(82)
11....	<i>o</i> -CH ₃ OC ₆ H ₄ —	C ₆ H ₅ CH ₂ —	169 (HCl)	(82, 288, 396)

TABLE 38—Concluded

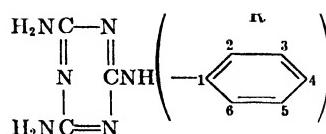
NO.	R	R'	MELTING POINT OF SALT OR BASE	REFERENCES
12.....	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{—}$	$\text{C}_6\text{H}_5\text{CH}_2\text{—}$	208 (HCl)	(82, 207, 285, 288, 396)
13.....	$o\text{-C}_2\text{H}_5\text{OC}_6\text{H}_4\text{—}$	$\text{C}_6\text{H}_5\text{CH}_2\text{—}$	188 (HCl)	(82, 207, 285, 288, 396)
14.....	$p\text{-C}_2\text{H}_5\text{OC}_6\text{H}_4\text{—}$	$\text{C}_6\text{H}_5\text{CH}_2\text{—}$	218 (HCl)	(207, 285, 288, 396)
15.....	$p\text{-ClC}_6\text{H}_4\text{O—}$	$\text{C}_6\text{H}_5\text{CH}_2\text{—}$	244 (HCl)	(82, 84, 207, 396)
16.....	$\text{C}_6\text{H}_5\text{—}$	$p\text{-ClC}_6\text{H}_4\text{CH}_2\text{—}$	277 (HCl)	(82, 84, 207)
17.....	$\text{C}_6\text{H}_5\text{—}$	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{—}$	212 (HCl)	(82, 84, 207)
18.....	$p\text{-ClC}_6\text{H}_4\text{—}$	$p\text{-ClC}_6\text{H}_4\text{CH}_2\text{—}$	264 (HCl)	(82, 84, 207)
19.....	$\text{C}_6\text{H}_5\text{—}$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{—}$	222 (HCl)	(82, 84, 207, 285)
20.....	$1\text{-C}_{10}\text{H}_7\text{—}$	$\text{C}_6\text{H}_5\text{CH}_2\text{—}$	209 (HCl)	(82, 207, 285, 288, 396)
21.....	$2\text{-C}_{10}\text{H}_7\text{—}$	$\text{C}_6\text{H}_5\text{CH}_2\text{—}$	232 (HCl)	(82, 84, 207)
22.....	$p\text{-C}_6\text{H}_5\text{OC}_6\text{H}_4\text{—}$	$\text{C}_6\text{H}_5\text{CH}_2\text{—}$	213 (HCl)	(82, 84, 207)



NO.	R	R'	n	MELTING POINT OF SALT	REFERENCES
23.....	$\text{C}_6\text{H}_5\text{—}$	$\text{C}_6\text{H}_5\text{CH}_2\text{—}$	2	116 (HCl)	(207, 288, 396)
24.....	$o\text{-CH}_3\text{OC}_6\text{H}_4\text{—}$	$\text{C}_6\text{H}_5\text{CH}_2\text{—}$	2	169 (HCl)	(285)
25.....	$\text{C}_6\text{H}_5\text{—}$	$\text{C}_6\text{H}_5\text{CH}_2\text{—}$	3	195 (HCl)	(82, 207, 285, 288, 396)

NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	REFERENCE
26.....	$ \begin{array}{c} \text{C}_6\text{H}_5\text{NCH}_2 \text{---} \text{N} \text{---} \text{H}_2 \\ \diagup \quad \quad \quad \diagdown \\ \text{HN} \quad \quad \quad \text{H}_2 \\ \quad \quad \quad \\ \text{H}_2 \quad \quad \quad \text{H}_2 \\ \quad \quad \quad \\ \text{CH}_2 \text{---} \text{C}_6\text{H}_5 \end{array} $	192–195/2.5 mm.	212 (HCl)	(230)

TABLE 39
Anilino-s-triazines (4,6)



NO.	R	MELTING POINT °C.	YIELD per cent
1.	H	284-286	82
2.	2-CH ₃	211-212	81
3.	3-CH ₃	229-230	82
4.	4-CH ₃	265-266	80
5.	2,4-(CH ₃) ₂	239-241	92
6.	2,5-(CH ₃) ₂	237-239	89
7.	2-Cl	205-208	81
8.	3-Cl	173-174	98
9.	4-Cl	245-249	82
10.	2,4-Cl ₂	255-257	86
11.	2,5-Cl ₂	228-230	84
12.	3,4-Cl ₂	210-211	98
13.	2-OH	257-259	87
14.	3-OH	241-242	76
15.	4-OH	282-283	88
16.	2-OC ₂ H ₅	203-205	76
17.	3-OC ₂ H ₅	211-212	82
18.	2-NO ₂	300	
19.	3-NO ₂	144-145	99
20.	4-NO ₂	300	
21.	2-COOH	Indefinite	42
22.	3-COOH	304-306	42
23.	4-COOH	300	68
24.	4-COCH ₃		98



NO.	GROUP IN POSITION 2	GROUP IN POSITION 4	GROUP IN POSITION 6	MELTING POINT °C.	YIELD per cent
25.	-NH ₂	-NH ₂	Naphthylamino	>300	75
26.	-NH ₂	-NH ₂	N-Methylanilino	257-259	97
27.	--NH ₂	-NH ₂	N-Ethylanilino	215-217	94
28.	-NH ₂	-NH ₂	N-Benzylanilino	311-314	99
29.	-NH ₂	-NH ₂	Piperidino	216-217	22
30.	-NH ₂	-NH ₂	Morpholino	236-240	48
31.	-NH ₂	-NHCH ₃	Anilino	84-86	48
32.	-NH ₂	-NHC ₂ H ₅	Anilino	153-155	49

TABLE 39—Concluded

NO.	GROUP IN POSITION 2	GROUP IN POSITION 4	GROUP IN POSITION 6	MELTING POINT °C.	YIELD
				per cent	
33.	—NH ₂	—NHCH ₂ C(CH ₃)=CH ₂	p-Chloroanilino·HCl	237-239	64
34.	—NH ₂	—NHCH ₂ C(CH ₃)=CH ₂	p-Toluidino	137-139	60
35.	—NH ₂	—NHC ₂ H ₄ OH	Anilino	156-158	76
36.	—NH ₂	—NHC ₂ H ₄ OH	m-Chloroanilino	147-150	43
37.	—NH ₂	—NHC ₂ H ₄ OH	p-Chloranilino	173-174	40
38.	—NH ₂	—NIICH ₂ CHOHCH ₃	Anilino	138-140	
39.	—NH ₂	—N(CH ₃) ₂	<i>o</i> -Chloroanilino	133-135	50
40.	—NH ₂	—N(CH ₃) ₂	<i>p</i> -Chloroanilino	173-175	50
41.	—NH ₂	—N(CH ₂ CH=CH ₂) ₂	<i>p</i> -Chloroanilino	137-141	
42.	—NH ₂	—N(CH ₂ CH=CH ₂) ₂	p-Toluidino	119-121	60
43.	—NH ₂	—N[CH ₂ C(CH ₃)=CH ₂] ₂	<i>o</i> -Chloroanilino	78-81	44
44.	—NH ₂	—N[CH ₂ C(CH ₃)=CH ₂] ₂	<i>p</i> -Chloroanilino	154-157	
45.	—NIICH ₃	—NIICH ₃	2,5-Dichloro-anilino	153-155	76
46.	—NHC ₂ H ₅	—NHC ₂ H ₅	Anilino·2HCl	178-180	70
47.	—NIIC ₂ H ₅	—NIIC ₂ H ₅	<i>m</i> -Chloroanilino·HCl	165-167	95
48.	—NIICH ₂ CH=CH ₂	—NIICH ₂ CH=CH ₂	<i>o</i> -Chloroanilino	56-59	
49.	—NIICH ₂ CH=CH ₂	—NIICH ₂ CH=CH ₂	<i>p</i> -Chloroanilino	103-106	66
50.	—NHC ₂ H ₅ OH	—NHC ₂ H ₅ OH	Anilino	130-132	
51.	—NHCH ₂ CHOHCH ₃	—NIICH ₂ CHOHCH ₃	Anilino·HCl	150-152	
52.	—NHCH ₂ COOH	—NIICH ₂ COOII	Anilino·3H ₂ O		
53.	—N(CH ₃) ₂	—N(CH ₃) ₂	<i>o</i> -Chloroanilino	114-117	43
54.	—N(C ₂ H ₅) ₂	—N(C ₂ H ₅) ₂	Anilino	87-89	90
55.	—N(C ₂ H ₅) ₂	—N(C ₂ H ₅) ₂	<i>p</i> -Chloroanilino	134-135	76
56.	—NH ₂	—N(C ₆ H ₅)C ₂ H ₄ OH	—N(C ₆ H ₅)C ₂ H ₄ OH	158-159	10
57.	—NH ₂	—Cl	4-Carboxy-3-hydroxyanilino	263-266	54

TABLE 40
*Rhône-Poulenc N-monoheterocyclic alkylenediamines (443)*Ethylenediamines: RNCH₂CH₂N(CH₃)₂

R'

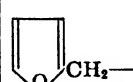
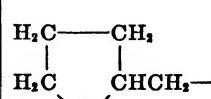
RHÔNE-POULENC CODE NO.	R	R'	ANTIHISTAMINE ACTIVITY	
			Aerosol*	Spasm
RP 2740	C ₆ H ₅ —		mg./kg. Inactive	
RP 2747	C ₆ H ₅ —		1	1†
RP 2749	C ₆ H ₅ —		20	

TABLE 40—Continued

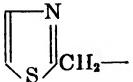
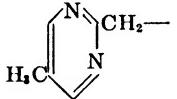
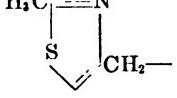
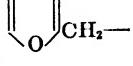
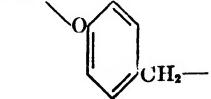
RHÔNE-POULENC CODE NO.	R	R'	ANTIHISTAMINE ACTIVITY	
			Aerosol*	Spasm
RP 2750		C ₆ H ₅ CH ₂ —	mg./kg. 0.5	1.3‡
RP 2758	C ₆ H ₅ —			
RP 2764	C ₆ H ₅ —		1	1/1.6†
RP 2765	C ₆ H ₅ —			
RP 2786		p-CH ₃ OC ₆ H ₄ CH ₂ —	0.1	1‡
RP 2788	C ₆ H ₅ —			
RP 2796		—CH ₂ CH ₂ OC ₂ H ₅		
KP 2803			0.5	1/6‡
RP 2833			5	1/8‡
RP 2843		p-C ₂ H ₅ OC ₆ H ₄ CH ₂ —	0.5	1‡

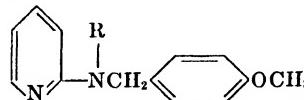
TABLE 40—Continued

RHÔNE-POULENC CODE NO.	R	R'	ANTIHISTAMINE ACTIVITY	
			Aerosol*	Spasm
RP 2855		<i>o</i> -CH ₃ OCH ₂ H ₄ CH ₂ —	mg./kg. 10	1/20‡
RP 2880	C ₆ H ₅ —			
RP 2890		C ₆ H ₅ CH ₂ —		
RP 2892		3,4-(CH ₃ O) ₂ C ₆ H ₃ CH ₂ —	Inactive	1/80‡
RP 2895	C ₆ H ₅ —			
RP 2909		<i>p</i> -CH ₃ OCH ₂ H ₄ CH ₂ —	10	
RP 2910		<i>p</i> -C ₆ H ₅ C ₆ H ₄ CH ₂ —	10	
RP 2914		<i>p</i> -CH ₃ OCH ₂ H ₄ CH ₂ —		
RP 2932		<i>p</i> -CH ₃ C ₆ H ₄ CH ₂ —		1
RP 2933	CH ₃ 	<i>p</i> -CH ₃ OCH ₂ H ₄ CH ₂ —		

TABLE 40—*Concluded*

RHÔNE-POULENC CODE NO.	R	R'	ANTIHISTAMINE ACTIVITY	
			Aerosol*	Spasm
RP 2938		p-CH ₃ OC ₆ H ₄ CH ₂ -	mg./kg. 10	
RP 2958		p-CH ₃ OC ₆ H ₄ CH ₂ -	50	
RP 2971		C ₆ H ₅ CH ₂ -	25	
RP 2972	C ₆ H ₅ -		25	
RP 3325		m-CH ₃ OC ₆ H ₄ CH ₂ -	Inactive	0‡
RP 3407		C ₆ H ₅ -		

Other N-heterocyclic alkylenediamines



RHÔNE-POULENC CODE NO.	R	ANTIHISTAMINE ACTIVITY	
		Aerosol*	Spasm
RP 2800	—CH ₂ CH ₂ CH ₂ N(CH ₃) ₂	2	1/10‡
RP 3420	—CH ₂ CH(CH ₃)N(CH ₃) ₂	1	1/4‡
RP 3427	—CH(CH ₃)CH ₂ N(CH ₃) ₂		

* Antihistamine dose to prevent bronchospasm in guinea pigs by inhalation of an aerosol of histamine (in milligrams per kilogram subcutaneously).

† Antihistamine activity on the isolated intestine of the guinea pig. Antergan = 1.

‡ Antihistamine activity on the isolated intestine of the guinea pig. Neoantergan = 1.

TABLE 41
Pyridine derivatives



NO.	R	BOILING POINT °C.	MELTING POINT OF SALT °C.	ANTIHISTAMINE ACTIVITY	TOXICITY L.D. 50	REFERENCES
1 (Pyribenzamine) . . .	C_6H_5-	177-179/0.13 mm. 167-172/0.1 mm. 193-205/2.0 mm. 138-142/0.01 mm. 185-190/1.7 mm.	170 (HBr) 195 (picrate)	0.02 ^(a)		(200)
2	$\text{C}_6\text{H}_5\text{CH}_2-$	195-200/4.0 mm. 131-141/0.02 mm.	143 (HCl) 162 (HCl)	$>10^{(a)}$	62 ^(b)	(112) (203) (193, 392) (256)
3	<i>p</i> -i-C ₄ H ₉ C ₆ H ₄ CH ₂ -	190-195/1.9 mm.				(193, 392)
4 (Neoantergan)	<i>p</i> -CH ₃ OC ₄ H ₄ -	168-172/0.06 mm. 185-190/2.0 mm.	143 (HCl) 135 (HCl) 131 (CH ₃ I)	0.02 ^(a)		(203)
5	3,4-(CH ₃ O) ₂ C ₆ H ₄ -	200-205/2 mm.	180 (HCl)			(230)
6	<i>p</i> -i-C ₄ H ₉ OC ₆ H ₄ -	194-195/0.20 mm.	152 (HCl)	60 ^(c)	18.5 ^(d)	(25)
7	<i>p</i> -FC ₆ H ₄ -	130-145/0.25 mm.	53 (base)	3-4 ^(e)		(442)
8	<i>p</i> -ClC ₆ H ₄ -	145-170/1.0 mm.	170 (HCl) 173 (HCl)	2-3 ^(e)		(442)

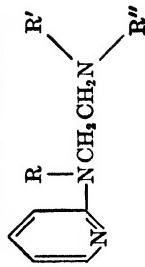
9.....	<i>o</i> -ClC ₆ H ₄ —	161-164/1.0 mm.	204 (HCl)	<0.5 ^(e)	(442)
10.....	<i>p</i> -BrC ₆ H ₄ —	184-190/0.5-1.0 mm.	186 (HCl)	160 ^(b)	(442)
11.....	<i>m</i> -BrC ₆ H ₄ —	176-178/1.0 mm.	170 (HCl)	<0.5 ^(e)	(256)
12.....	<i>p</i> -IC ₆ H ₄ —	194-207/1.0 mm.	195 (HCl)	0.3-0.5 ^(e)	(442)
13.....	Cyclo-C ₆ H ₁₁ —H	160-165/13 mm.	226 (HCl)		(230)
14.....		132-138/1.5 mm.			(112)
15.....	<i>n</i> -C ₆ H ₉	116-121/2 mm.	127 (HCl)		(392)
16.....	(CH ₃) ₂ NCH ₂ —	103-107/0.04 mm.	225 (3HCl)	>10 ^(a)	(203)
17.....	<i>n</i> -C ₆ H ₁₃	136-146/1 mm.	105 (HCl)	Inactive	(442)
18 (Foralaminin).		106-108/0.02 mm. 117-118/0.2 mm. 136-137/0.7 mm.	164 (HCl) 119 (HCl) 97 (dihydrogen citrate)	76 ^(c) 110 ^(f) 106 ^(g)	19.0 ^(d) (25) (229)
19.....		108-111/0.2 mm. 129-152/2.0 mm.	142 (fumarate) 109 (fumarate)	126 ^(b) 106 ^(g)	126 ^(b) (441)
20.....		156-158/0.5 mm. 135-140/0.4 mm.	107 (dihydrogen citrate) 136 (fumarate)	>100 ^(b) 203 ^(g)	ca. 230 ^(b) (441)
21 (Histadyl, Thenylenec)		173-175/3.0 mm.	163 (HCl) 157 d. (CH ₃ I)	100 ^(e) 206 ^(b)	(452) (452)
		185-186/8.0 mm. 123-135/0.1 mm. 166-168/2.0 mm.	161 (HCl) 165 (HCl) 163 (HCl)	1-10 ⁽ⁱ⁾	(228) (90) (242)

TABLE 41—Continued

NO.	R	BOILING POINT °C.	MELTING POINT OF SALT °C.	ANTIHISTAMINE ACTIVITY	TOXICITY L.D. ₅₀	REFERENCES
22.....		185-190/2 mm.				(392)
23.....		185-190/3.5 mm.	146 (HCl)	0.01-0.1 ⁽ⁱ⁾	(90)	
24 (Chlorothen).....		171-173/1.8 mm. 155-156/1 mm.	111 (HCl) 108 (HCl) 106 (dihydrogen phosphate) 118 (dihydrogen citrate)	10-100 ⁽ⁱ⁾ 10-100 ⁽ⁱ⁾ 10-100 ⁽ⁱ⁾	230 ^(b) (88, 90) (90)	
25 (Bromothen).....		173-175/1 mm.	126 (HCl)	10-100 ⁽ⁱ⁾	230 ^(b) 130 ^(b)	(88, 90) (256)
26.....			185 (HCl)	0.1-1.0 ⁽ⁱ⁾	(90)	
27.....		150-160/0.001 mm.	209 (HCl)	0.01-0.1 ⁽ⁱ⁾	(90)	

28.....		174-180/1.0 mm. 179-181/1.0 mm.	170 (HCl)	0.1-1.0 ⁽ⁱ⁾	(90) (62)
29 (Thenfadil)		169-172/1.0 mm.	170 (HCl)	8.3 ^(j) 17.5 ^(k)	(62, 235)
30.....		177-179/1 mm.		7.9 ^(l) 18.0 ^(k)	(62, 235)
31.....		156-158/1 mm.		7.2 ^(j) 21.0 ^(k)	(62, 235)
32.....		200 (dipicrate)	0.01-0.1 ⁽ⁱ⁾	(90)	
33.....		185-190/2 mm.			(193)
34.....		200/1 mm.	95 (base) 226 (HCl)	Inactive	(442)

TABLE 41—Continued



No.	R	R'	R''	BOILING POINT		MELTING POINT OF SALT °C.	ANTIHISTAMINE ACTIVITY	REFERENCES
				°C.	°C.			
35.....	C ₂ H ₅	CH ₃	CH ₃	99-104/0.04 mm.	112 (HCl)	1(a)	(203)	
36.....	i-C ₃ H ₇	CH ₃	CH ₃	120-125/1 mm.	226 (HCl)	>10(a)	(112, 203)	
37.....	n-C ₃ H ₇	C ₂ H ₅		151-155/13 mm.			(203)	
38.....	C ₂ H ₅ OCH ₂ CH ₂ -	CH ₃		160-165/1.7 mm.			(393)	
39.....	C ₆ H ₅ -	CH ₃		185-187/14 mm.			(203)	
40.....	C ₆ H ₅ -	C ₂ H ₅		135-149/0.08 mm.			(112)	
		C ₂ H ₅ -		145-150/0.08 mm.				
41.....	C ₆ H ₅ CH ₂ -	H		145-150/0.08 mm.	136 (HCl)	>10(a)	(203)	
42.....	C ₆ H ₅ CH ₂ -	CH ₃			158 (sulfate)		(156)	
43.....	C ₆ H ₅ CH ₂ -	C ₂ H ₅		155-156/0.075 mm.			(25)	
		C ₂ H ₅		142-150/0.02 mm.			(203)	
44.....	p-i-C ₃ H ₇ C ₆ H ₄ CH ₂ -	CH ₃		194-195/0.20 mm.	206 (2HCl)	>5(a)	(25)	
45.....	C ₆ H ₅ CH ₂ CH ₂ -	CH ₃		131-141/0.02 mm.	152 (HCl)	60(a)	(203)	
46.....	C ₆ H ₅ CO-	CH ₃		150-152/0.01 mm.	162 (HCl)	>10(a)	(203)	
		CH ₃			154 (HCl)	>5(a)	(203)	
47.....		CH ₃		126-130/0.01 mm.	181 (2HCl)		(203)	
48.....		C ₂ H ₅		136-140/0.04 mm.	192 (2HCl)	>10(a)	(203)	

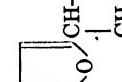
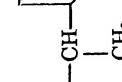
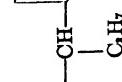
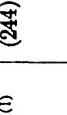
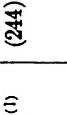
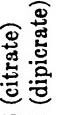
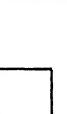
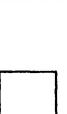
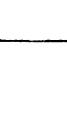
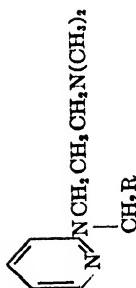
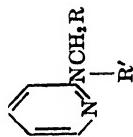
49.....		CH ₃	138-143/0.03 mm.	>10 ^(a)	(112, 203)
50.....		CH ₃	121-126/1.0 mm.	136 (fumarate) 2 ^(a)	(187)
51.....		CH ₃	150-151/1 mm.	173 (HCl) 0.1-1.0 ^(b)	(90)
52.....		CH ₃	130-135/0.5 mm.	0.1-1.0 (90)	
53.....		C ₂ H ₅	157-160/2 mm.	145 (2HCl) (228)	
54.....			193-198/0.2 mm.	171 (2HCl) 1/4 ^(b)	(244)
55.....			178-179/0.45 mm.	151 (citrate) <1/100 ^(b)	(244)

TABLE 41—Continued

No.	R	R'	R"	BOILING POINT °C.	MELTING POINT OF SALT °C.	ANTIHISTAMINE ACTIVITY	REFERENCES
56.....				149-153/0.25 mm.	138 (citrate) 154 (dipicrate)	1/10 ⁽¹⁾	(244)
57.....				155-165/0.5 mm.	113 (citrate)	1/10 ⁽¹⁾	(244)
58.....				168-172/0.1 mm.	118 (citrate)	1/6 ⁽¹⁾	(244)
59.....			Cl	122-126/0.01 mm.	187 (HCl)		(203)
60.....	C ₂ H ₅			170-180/0.02 mm.	176 (HCl)	>2 ^(a)	(203)
61.....	C ₄ H ₉ CH ₂ -			189-194/1 mm.	136 (HCl)		(242)
62.....				174-180/0.03 mm.	206 (2HCl)		(203)



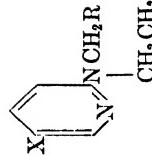
NO.	R	BOILING POINT		MELTING POINT OF SALT °C.	REFERENCES
		"C.	mm.		
63.....	C ₄ H ₉ —	200–205/3	mm.	(193, 392)	
64.....	p-CH ₃ OCH ₂ H,—	195–200/2.5	mm.	(193, 392)	
65.....		171–174/4	mm.	124 (HCl) (242)	

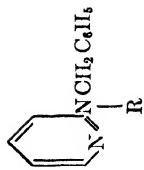


NO.	R	R'	BOILING POINT		MELTING POINT OF SALT °C.	ANTI-HISTAMINE ACTIVITY	REFERENCES
			"C.	mm.			
66.....	(C ₄ H ₉) ₂ C—	(CH ₃) ₂ NCH ₂ CH ₃ —	175–177/2	mm.	185 (2HCl)	0.4 ⁽¹⁾	(402)
67.....	(C ₄ H ₉) ₂ C—	(C ₂ H ₅) ₂ NCH ₂ CH ₃ —	190–195/2	mm.	205 (2HCl)	0.04–0.08 ⁽¹⁾	(403)
68.....		(CH ₃) ₂ NCH(CH ₃)CH ₃ —	162–169/1.5	mm.	102 (bisuccinate)		(242)
69.....	C ₄ H ₉ —	(C ₄ H ₉) ₂ NCH ₂ C(CH ₃) ₂ CH ₃ —					(112)

TABLE 41—Continued

NO.	X	R	BOILING POINT °C.	MELTING POINT OF SALT ANTIHISTAMINE ACTIVITY		L.D.50	REFERENCES
				°C.			
70.....	Br	C ₆ H ₅ —	145-146/0.02 mm.	182 (HCl)	<0.5 ^(e)		(442)
71.....	Cl	C ₆ H ₅ —	163-185/0.02-0.05 mm.	180 (HCl)	58 ^(e)	15.0(d)	(25)
72.....	Br	m-BrC ₆ H ₄ —		180 (HCl)	<0.5 ^(e)		(442)
73.....	Cl	p-CH ₃ OOC ₆ H ₄ —	180-185/0.05 mm.	147 (HCl)	<0.5 ^(e)		(442)
74.....	Br		175-185/0.6 mm.	142 (HCl)	34 ^(e)	26.0(d)	(25)
75.....	Br			141 (HCl)	0.1-1.0 ⁽ⁱ⁾		(90)
76.....	Br		175-190/0.0001 mm.	166 (HCl)	0.01-1.0 ⁽ⁱ⁾		(90)
77.....	Br			137 (HCl)	0.1-1.0 ⁽ⁱ⁾		(90)
				176 (HCl)	0.01-1.0 ⁽ⁱ⁾		(90)





No.	R	BOILING PT.		MELTING POINT OF SALT °C.	ANTIHISTAMINE ACTIVITY	REFERENCES
		°C.	°C.			
78.....	$-\text{CH}_2\text{CON}(\text{CH}_3)_2$			184 (HCl)	Inactive	(442)
79.....	$-\text{CH}_2\text{CON}(\text{C}_2\text{H}_5)_2$			148 (HCl)	Inactive	(442)
80.....		163-164/0 1 mm.				(341, 343)
81.....				155-156/0.2 mm.		(341, 343)
82.....				163 d. (dipicrate)		(341)
83.....						(341)

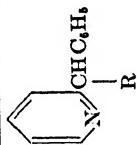
TABLE 41—Continued

NO.	R	BOILING POINT		MELTING POINT OF SALT °C.	ANTIHISTAMINE ACTIVITY	REFERENCES
		°C.				
84.....						(341)
85.....		188-189/0.5 mm.		260 (3HCl)		(341, 342)
86.....		188-194/0.3-0.6 mm.		225 d. (dipicrate)	0.75 ^(m)	(341, 342)
87.....						(341)
88.....						(341)
89.....						(341)

NO.	R	R'		MELTING POINT OF SALT °C.	REFERENCES
90.....				160 (picrate)	(70)
91.....				87 (HCl)	(70)
92.....				110 (HCl)	(70)



No.	R	BOILING POINT		MELTING POINT OF SALT °C.	REFERENCES
		°C.	mm.		
93.....	H	114-116	1.4 mm.	276 (2HCl) 259	(184)
94.....	CH ₃	106-107	2.7 mm.	259 (2HCl)	(184)
95.....		135-140	1.4 mm.	283 (2HCl)	(184)



No.	R	BOILING POINT		MELTING POINT OF SALT OR BASE °C.	ANTIHISTAMINE ACTIVITY	REFERENCES
		°C.	mm.			
96.....	-NHCH ₂ CH ₂ N(CH ₃) ₂	140-143	0.5 mm.	175 (HCl)	5.0 ^a	(423)
97.....	-N(CH ₃)CH ₂ CH ₂ N(CH ₃) ₂	160-163	1.0 mm.	140 (HCl)	20.0 ^{a,b}	(423)
98.....	-NCH ₂ CH ₂ N(CH ₃) ₂	185-190	0.2 mm.	178 (HCl)	5.0 ^a	(423)
99.....					94 (base)	(183)

TABLE 41—Continued
 $R-N(CH_2CH_2N(CH_3)_2$

NO.	R	R'	BOILING POINT °C.	MELTING POINT OF SALT ANTIHISTAMINE ACTIVITY	REFERENCES
100.....		C_6H_5-	161-165/0.08 mm.	204 (2HCl) °C. $>10^{(a)}$	(203)
101.....		$C_6H_5CH_2-$	150-160/0.02 mm.	170 (HCl) 1.0 ^(a)	(203)
102.....		H	125-144/13 mm.		(112)
103.....		$C_6H_5CH_2-$	185-188/14 mm.	241 (2HCl) 2 ^(a)	(112, 203)
104.....		$C_6H_5CH_2-$ CH ₃	156-161/0.18 mm.	176 (HCl) 0.2 ^(a)	(203)

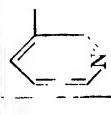
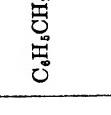
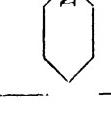
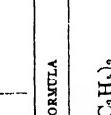
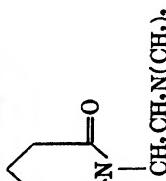
105		98-100/0.04 mm.	137 (HCl)	>5.0 ^(a)	(203)
106					(112)
107					(112)
108	 FORMULA: $\text{C}_2\text{H}_5\text{N}(\text{CH}_3)_2\text{CH}_2\text{N}$	112-113/0.03 mm.	10 ^(a)	(203)	
109					(112)
110		165-170/2 mm.	217 (HCl)	Inactive	(228)

TABLE 41—Concluded

NO.	R	R'	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY ^a	REFERENCES
	FORMULA	FORMULA				
111.....		$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	138/7 mm.	131 (picrate) 252 (CH ₃ I)	(307)	

(a) Micrograms of compound per milliliter of bath liquid capable of neutralizing the contraction of an isolated guinea-pig gut caused by 1 γ/ml. of histamine diphosphate.

(b) Intraperitoneally (milligrams per kilogram).

(c) Average per cent by which a bath concentration of 9.375×10^{-5} μg./ml. of antihistaminic reduced the response of guinea-pig ileum to a histamine base concentration of 0.024 μg./ml. Pyribenzamine = 37; Benadryl = 17.

(d) Acute toxicity (milligrams per kilogram) to rats (intravenous injection).

(e) Spasmolytic index when tested on the isolated guinea-pig ileum by the method of Litchfield and coworkers (256).

(f) Activity by histamine aerosol technique. Pyribenzamine = 100.

(g) Relative activity on the basis of Pyribenzamine = 100: Based on the amount of drug, on a free-base basis, that on the average produced a 50 per cent relaxation of a maximal histaminic spasm of the isolated strip of guinea-pig ileum.

(h) Acute toxicity, on a free-base basis, for 50 per cent mortality in 24 hr. after oral dosing in male white mice (milligrams per kilogram).

(i) H ratio = micrograms of histamine to produce a given contraction per microgram of compound required to suppress this response.

Determined on the isolated guinea-pig gut.

(j) Spasmolytic potency expressed as the log of the effective dilution as determined by Miller, Becker, and Tainter (289). Values represent the concentration of base. Pyribenzamine = 7.4; Thenylene = 7.7.

(k) Intravenously in milligrams of base per kilogram.

(l) Spasmolytic index compared to Pyribenzamine = 100.

(m) Spasmolytic activity compared to Benadryl = 1.

(n) Minimum dose of compound necessary to antagonize 0.1 γ/ml. of histamine diphosphate on isolated guinea-pig intestine. Pyribenzamine = 0.01.

TABLE 42
Pyrimidine derivatives

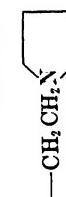
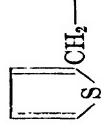
NO.	R	R'	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
						
1.....	—CH ₂ CH ₂ N(CH ₃) ₂		131-133/0.05 mm.	177 (HCl)	10*	(25)
2.....	—CH ₂ CH ₂ N— 		180-181/0.23 mm.	126 (citrate)	1/10-1/30†	(244)
3 (Heteramine)	—CH ₂ CH ₂ N(CH ₃) ₂	C ₆ H ₅ — 	148-155/3.0 mm.	198 (HCl) 212 (HCl)		(193, 392) (150)
4 (Neohetramine)	p-CH ₃ OCH ₂ H ₄ —		185-187/2.2 mm.			(150)
5	p-CH ₃ OCH ₂ H ₄ —	—CH ₂ CH ₂ N(C ₂ H ₅) ₂		113 (HCl)		(112)
6	p-CH ₃ OCH ₂ H ₄ —	—CH ₂ CH ₂ N— 	203-206/0.6 mm.	136 (HCl)	1/30-1/60†	(244)

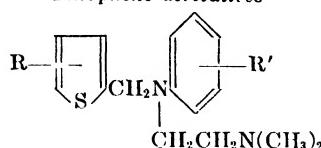
TABLE 42—*Concluded*

NO.	R	R'	BOILING POINT	MELTING POINT OF SAL. ^a	ANTIHISTAMINE ACTIVITY	REFERENCES
						
7.....	4-CH ₃		147-148, 1.2 mm.	143 (HCl)		(230)
8.....	4-CH ₃	C ₆ H ₅ CH ₂ -	138/1.4 mm.			(150)
9.....	4-OCH ₃	C ₆ H ₅ CH ₂ -	141-143, 0.04 mm.	166 (HCl)	36*	(25)
10.....	4,6-(CH ₃) ₂	C ₆ H ₅ CH ₂ -	117/1.7 mm.	165 (HCl)		(150, 193, 302)
11.....	H	2,4-(CH ₃) ₂ C ₆ H ₃ -				(112)

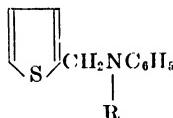
* Average per cent by which a bath concentration of 9.375×10^{-5} $\mu\text{g./ml.}$ of antihistaminic reduced the response of guinea-pig ileum to a histamine base concentration of $0.024 \mu\text{g./ml.}$ Pyribenzamine = 37; Benadryl = 17.

† Spasmolytic index compared to Pyribenzamine = 100.

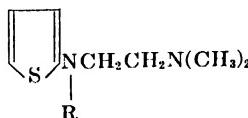
TABLE 43
Thiophene derivatives



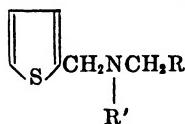
NO.	R	R'	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
			°C.	°C.		
1(Diatrin).	H	H	183 185/7 mm. 185-186/8 mm.	187 (HCl) 184 (HCl)	1* 2/3*	(131, 242) (228)
2 . . .	H	2-Cl	175-176/3.5 mm.	185 (HCl)	Inactive	(230)
3. . . .	H	3-Cl	190-191/3.5 mm.	165 (HCl)	Slight	(230)
4	H	4-Cl	184-186/1.5 mm.	187 (HCl)	1/2*	(230)
5. . . .	H	4-OCH ₃	175-180/1.5 mm.	148 (HCl)		(230)
6	5-Cl	H	171/2 mm.	164 (HCl)	1.25*	(230)
7. . . .	5-Cl	2-Cl	184-186/2 mm.	144 (HCl)		(230)
8	5-Cl	3-Cl	195-197/2 mm.	168 (HCl)		(230)
9. . . .	5-Cl	4-Cl	197-200/2 mm.	188 (HCl)		(230)
10. . . .	5-C' <td>4-OCH₃</td> <td>178/1.5 mm.</td> <td>110 (HCl)</td> <td></td> <td>(230)</td>	4-OCH ₃	178/1.5 mm.	110 (HCl)		(230)



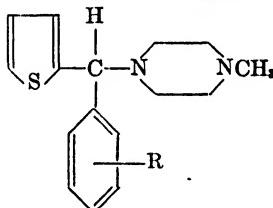
NO.	R	BOILING POINT	MELTING POINT OF SALT	ANTIHIS-TAMINE ACTIVITY	REFER-ENCES
		°C.	°C.		
11 . .	--CH ₂ CH ₂ N(C ₂ H ₅) ₂	157-160/2 mm.	145 (2HCl)	1/5*	(228)
12 . .	--CH ₂ CH(CH ₃)N(CH ₃) ₂	164-171/3 mm.	100 (bisuccinate)		(242)
13 . .	--CH ₂ CH ₂ N	198-199/1.3 mm.	130 (citrate)	1/10-1/15†	(244)
14 . .	--CH ₂ CH ₂ N	215-218/5 mm.	188 (HCl)		(242)



NO.	R	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
		°C.	°C.		
15 . . .	CH ₃	83-92/4 mm.	231 d. (HCl)	Inactive	(230)
16 . . .	C ₂ H ₅				(112)

TABLE 43—*Concluded*

NO.	R	R'	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
17...			°C. 167-170/0.25 mm.	°C. 100 (citrate) 177 (dipicrate)	1/100†	(244)
18...				178 d. (HCl)	Inactive	(63, 230)
19...			°C. 153-154/0.2 mm.	97 (citrate)	<1/100†	(244)

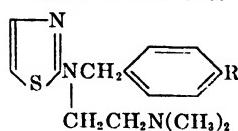


NO.	R	MELTING POINT OF SALT	REFERENCES
20	H	°C. 202 d. (2HCl)	(183)
21	4-Cl	216 d. (oxalate)	(183)

* Activity compared to Antergan = 1.

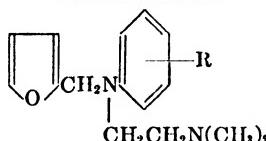
† Spasmolytic index compared to Pyribenzamine = 100.

TABLE 44
Thiazole derivatives



NO.	R	MELTING POINT OF SALT °C.	REFERENCES
1.....	H	172 (HCl) 141 (picrate)	(222)
2.....	CH ₃ O		(400)
3.....	Cl	164 (HCl) 151 (HCl)	(222)

TABLE 45
Furan derivatives



NO.	R	BOILING POINT	MELTING POINT OF HYDRO- CHLORIDE °C.	ANTIHISTAMINE ACTIVITY	L.D. ₅₀	REFERENCES
1.....	H	127-129/0.05 mm.	148	70*	30.0†	(25)
2.....	4-i-C ₄ H ₉	130-131/0.04 mm.	139	20*	9.4†	(25)
3.....	4-Methoxy	155-156/0.075 mm.	126	3*	35.0†	(25)
FORMULA						
4.....			120 d.			(63)

* Average per cent by which a bath concentration of 9.375×10^{-5} $\mu\text{g./ml.}$ of antihistaminic reduced the response of guinea-pig ileum to a histamine base concentration of 0.024 $\mu\text{g./ml.}$ Pyribenzamine = 37; Benadryl = 17.

† Acute toxicity to rats, intravenously, in milligrams per kilogram.

TABLE 46
Piperidine derivatives



NO.	R	BOILING POINT °C.	MELTING POINT OF SALT °C.	ANTIHISTAMINE ACTIVITY	REFERENCES
1....	$-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$		293 (2HCl)	Inactive	(307, 323)
2....	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$			Inactive	(323)
3....	$-\text{CH}_2\text{CH}_2\text{N}$			Inactive	(323)
FORMULA					
4....		138/7 mm.	131 (picrate) 252 (CH3I)		(307)
5....	C_2H_5 	101-104/0.05 mm.	255 d. (dipicrate)		(342)
6....	C_2H_5 	167-189/0.8 mm.	200 d. (tripicrate)		(342)

TABLE 47
Pyrrolidone, pyrazine, and pyridazine derivatives

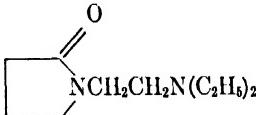
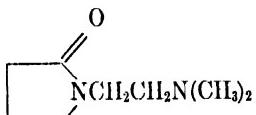
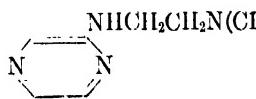
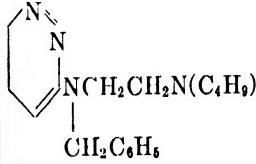
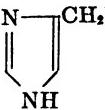
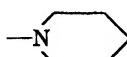
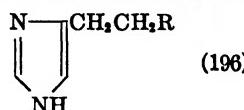
NO.	FORMULA	BOILING POINT °C. mm.	MELTING POINT OF SALT °C.	REFERENCE
1.	 $\text{NCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	122/4 mm.	94 (picrate)	(307)
2.	 $\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	118-122/20 mm.	156 (HCl) 282 (CH3I)	(307)
3.	 $\text{NHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	120-124/4 mm.	159 (picrate)	(112)
4.	 $\text{CH}_2\text{C}_6\text{H}_5$			(115)

TABLE 48
4-Alkylimidazoles

NO.	R	MELTING POINT OF SALT OR BASE	YIELD <i>per cent</i>
	 (432)		
1.....	—OH	91 (HCl)	85
2.....	—Cl	141 (HCl)	77
3.....	—CH ₂ N(CH ₃) ₂	198 (2HCl)	84
4.....	—CH ₂ N(C ₂ H ₅) ₂	193 (2HCl)	69
5.....		225 (2HCl)	69
6.....	—NCH ₂ C ₆ H ₅ CH ₃	209 (2HCl)	90
7.....	—NCH ₂ C ₆ H ₅ C ₂ H ₅	209 (HCl)	90
8.....	—N(CH ₂ C ₆ H ₅) ₂	149 (base)	84
9.....	—NCH ₂ C ₆ H ₅ C ₆ H ₅	148 (base)	
10.....	—NHCH ₃	199 (2HCl)	75
11.....	—NHC ₂ H ₅	170 (2HCl)	81
12.....	—NHCH ₂ C ₆ H ₅	201 (2HCl)	70
13.....	—SCH ₃	128 (HCl) 146 (picrate)	
14.....	—NH ₂	247 (2HCl)	



15.....	—N(CH ₃) ₂	184 (2HCl) 215 (dipicrate)	25
16.....	—NHC ₂ H ₅	163 (2HCl) 185 (dipicrate)	35
17.....	—NHC ₆ H ₅	100 (2HCl) 165 (dipicrate)	50

TABLE 48—Concluded

NO.	R	MELTING POINT OF SALT OR BASE	YIELD
		°C.	per cent
18.....	—NHCH(CH ₃) ₂	196 (2HCl) 175 (dipicrate)	35
19.....	—N(C ₂ H ₅) ₂	220 (2HCl)	15
20.....	—N(C ₂ H ₇) ₂	sirup (2HCl) 190 (dipicrate)	45
21.....		278 (2HCl) 191 (dipicrate)	55
22.....		243 (2HCl)	55
23.....	—NCH ₂ C ₆ H ₅ CH ₃	179 (2HBr)	20
24.....	—NCH ₂ C ₆ H ₅ C ₂ H ₅	83 (2HBr)	5
25.....	—N(CH ₂ C ₆ H ₅) ₂	156 (2HBr)	15
26.....	—OC ₆ H ₅	137 (HCl) 120 (picrate)	40
27.....		152 (base)	25

TABLE 49
N-Heterocyclic imidazolines and imidazoles

NO.	FORMULA	BOILING POINT °C.	MELTING POINT OF SALT °C.	REFERENCES
1.....	 $\text{C}_6\text{H}_5\text{NCH}_2\text{C}(\text{H}_2\text{C}-\text{S})=\text{N}-\text{CH}_2-\text{CH}_2-\text{Cl}$	190-200/0.4 mm.	220 (HCl)	(228)
2.....	 $\text{C}_6\text{H}_5\text{NCH}_2\text{C}(\text{H}_2\text{C}-\text{S})=\text{N}-\text{CH}_2-\text{CH}_2-\text{Cl}$		223 (HCl)	(230)
3.....	 $\text{N}-\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$		200 (2HCl)	(431)
4.....	 $\text{N}-\text{CH}_2\text{N}(\text{C}_6\text{H}_{11})$		227 (2HCl)	(431)
5.....	 $\text{N}-\text{CH}_2\text{N}(\text{C}_4\text{H}_8\text{O})$		173 (2HCl)	(431)
6.....	 $\text{N}-\text{CH}_2\text{C}=\text{NH}-\text{NH}_2$		230 (2HCl)	(431)

TABLE 50
N-Poly cyclic Rhône-Poulenc diamines (443)

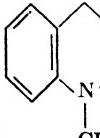
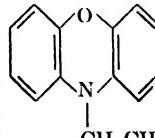
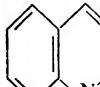
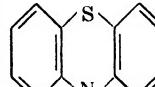
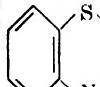
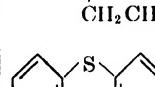
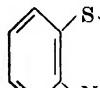
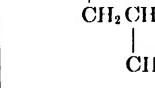
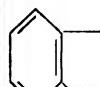
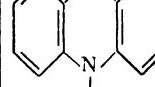
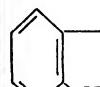
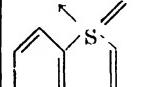
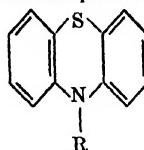
CODE NO.	FORMULA	CODE NO.	FORMULA
RP 2756..	 <chem>CN(C)C[C@H]1C=CC=CC=C1N</chem>	RP 3192..	 <chem>CN(C)C[C@H]1C=CC=CC=C1Nc2ccccc2</chem>
RP 2970..	 <chem>CN(C)C[C@H]1C=CC=CC=C1Nc2ccccc2</chem>	RP 3276..	 <chem>CN(C)C[C@H]1C=CC=CC=C1Nc2ccsc2</chem>
RP 2987..	 <chem>CN(C)C[C@H]1C=CC=CC=C1Nc2ccsc2</chem>	RP 3277..	 <chem>CN(C)C[C@H]1C=CC=CC=C1Nc2ccsc2C</chem>
RP 3015..	 <chem>CN(C)C[C@H]1C=CC=CC=C1Nc2ccccc2Nc3ccccc3</chem>	RP 3283..	 <chem>CN(C)C[C@H]1C=CC=CC=C1Nc2ccsc2C(=O)O</chem>
RP 3040..	 <chem>CN(C)C[C@H]1C=CC=CC=C1</chem>	RP 3289..	 <chem>CN(C)C[C@H]1C=CC=CC=C1Nc2ccccc2C(=O)S(=O)(=O)c3ccccc3</chem>
RP 3041..	 <chem>CN(C)C[C@H]1C=CC=CC=C1Cc2ccccc2</chem>	RP 3298..	 <chem>CN(C)C[C@H]1C=CC=CC=C1Nc2ccsc2CO</chem>
RP 3110..	 <chem>CN(C)C[C@H]1C=CC=CC=C1Cc2ccccc2</chem>		

TABLE 50—*Concluded*

CODE NO.	FORMULA	CODE NO.	FORMULA
RP 3299..		RP 3389..	
RP 3300..		RP 3390..	
RP 3349..		RP 3398..	

TABLE 51
10-Substituted phenothiazines



NO.	R	BOILING POINT °C.	MELTING POINT OF SALT OR BASE °C.	REFERENCES
1.....	-CH ₂ CH ₂ N(CH ₃) ₂	183-187/1 mm. 190-192/3 mm.	60 (base) 201 (HCl)	(146) (394)
2.....	-CH ₂ CH ₂ CH ₂ N(CH ₃) ₂	208-210/3 mm.	181 (HCl)	(394)
3.....	-CH ₂ CH ₂ N(C ₂ H ₅) ₂	200-205/1.1 mm.	175 (HCl)	(394)
4.....	-CH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂	213-215/1.5 mm.		(394)
5 (Phen- ergan)...	-CH ₂ C(CH ₃)N(CH ₃) ₂	190-192/3 mm.	204 (HCl) 207 (CH ₃ I) 275 (methyl benzenesul- fonate)	(394) (77)
6.....	-CH ₂ C(CH ₃) ₂ CH ₂ N(CH ₃) ₂	196-199/3 mm.	186	(394)
7.....	-CH ₂ CH ₂ N(CH ₃)CH ₂ CH ₂ OH		155 (CH ₃ Pr)	(99, 170)
8.....	-COCH ₂ N(CH ₃) ₂		116 (base)	(126)
9.....	-COCH ₂ N(C ₂ H ₅) ₂		59 (base)	(126)
10.....	--COCH ₂ N		165 (base)	(126)
11.....	--COCH ₂ N		126 (base)	(126)
12.....	--COCHN(C ₂ H ₅) ₂		100 (base)	(126)
13.....	--COCHN		111 (base)	(126)
14.....	--COCHN(CH ₃) ₂		99 (base)	(126)
15.....	--COCHN(C ₂ H ₅) ₂		203 d. (HCl)	(126)

TABLE 51—Continued

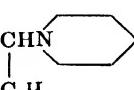
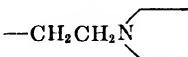
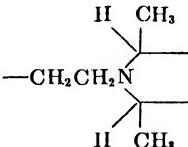
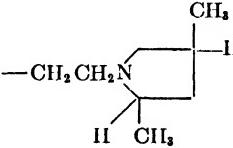
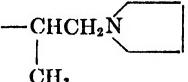
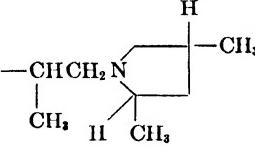
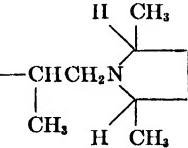
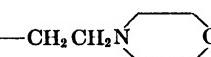
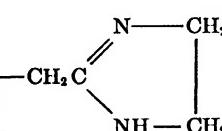
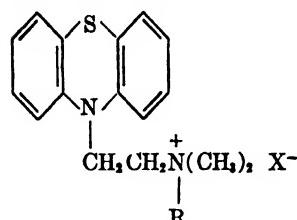
NO.	R	BOILING POINT °C.	MELTING POINT OF SALT OR BASE °C.	REFERENCES
16.....			216 d. (HCl)	(126)
17 (Pyrro-lazote) ..			197 (HCl)	(199, 338)
18.. . . .			196 (HCl)	(198, 338)
19..... .			162 (HCl)	(198, 338)
20.....			194 (HCl) 181 d. (oxa-late)	(198, 338)
21.....			250 (HCl)	(198, 338)
22.....			103 (base)	(198, 338)
23.....		210-212/2 mm.	170 (HCl)	(395)
24.....		229-232/2 mm.	185 (HCl)	(395)
25.....			243 (HCl)	(286)

TABLE 51—Continued

NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT OR BASE	REFERENCES
		°C.	°C.	
26.....		220-223/3 mm.	182 (HCl)	(394)
27.....		218-222/3 mm.		(394)
28.....			213 (HCl)	(286)
29.....				(95, 146)
30.....				(95, 146)

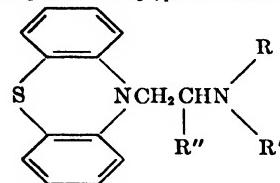
TABLE 51—*Concluded*

Quaternary ammonium bases derived from 10-substituted phenothiazines (78)



NO.	R	X	MELTING POINT °C.
31.....	-CH ₂ CH ₂ Br	Br	226
32.....	-CH ₂ CH ₂ CH ₂ CH ₂ Br	Br	218
33.....	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ Br	Br	195
34.....	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ Br	Br	186
35.....	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ Br	Br	150
36.....	-CH ₂ CH ₂ CH ₂ Cl	Cl	200
37.....	-CH ₂ CH ₂ CH ₂ CHBrCH ₃	Br	221
FORMULA			
38.....	 10-((10-((CH ₂) ₆ Br)Br)ethylamino)methyl-5,10-dihydrophenothiazine		140
39.....	 10-((CH ₃)(CH ₂) ₆ Br)ethylamino)methyl-5,10-dihydrophenothiazine		290

TABLE 52
N-(Dialkylaminoalkyl)phenothiazines (464)



NO.	R	R'	R''	BOILING POINT °C.	MELTING POINT OF SALT OR BASE °C.	ANTIHISTA- MINE ACTIVITY*
1...	CH ₃	<i>i</i> -C ₃ H ₇	H	168-172/0.1 mm.	179 (HCl)	3
2...	C ₃ H ₆	<i>i</i> -C ₃ H ₇	H	173 (HCl)	1/2	
3...	CH ₃	C ₃ H ₆ CH ₂ -	H	92 (base)	<1/100	
4...	CH ₃	<i>n</i> -C ₄ H ₉	H	185-195/0.7 mm.	144 (HCl)	1/3-1/2
5...	CH ₃	<i>i</i> -C ₃ H ₇	H	162-164/0.3 mm.	154 (HCl)	1/5
6...	CH ₃	CH ₂ =CHCH ₂ -	H	187-190/1.0 mm.	179 (HCl)	1.5-2
7...	C ₃ H ₆	CH ₂ =CHCH ₂ -	H	165-185/0.1 mm.	127 (HCl)	1/4
8...	CH ₂ =CHCH ₂ -	CH ₂ =CHCH ₂ -	H	220-223/2.6 mm.	126 (HCl)	<1/200
9...	CH ₃	<i>i</i> -C ₃ H ₇	C ₂ H ₅	70 (base)		1
10...	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	H	204-207/0.5 mm.	172 (HCl)	<1/2, >1/20
11...	<i>n</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇	H	203-209/0.7 mm.	202 (HCl)	<1/10
12...	<i>n</i> -C ₃ H ₇	CH ₂ =CHCH ₂ -	H	212-216/0.5 mm.	148 (HCl)	<1/20
13...	<i>i</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇	H	180-181/0.5 mm.	199 (HCl)	1/10
14...	<i>i</i> -C ₃ H ₇	CH ₂ =CHCH ₂ -	H	212-213/0.9 mm.	171 (HCl)	<1/2, >1/20
15...	C ₆ H ₅ CH ₂ -	C ₆ H ₅ CH ₂ -	H		200 (HCl)	
16...		<i>n</i> -C ₃ H ₇	H		148 (HCl)	

*Antihistamine activity determined on isolated strip of guinea-pig ileum. Benadryl 1; RP 3015 = 3-5; Pyrrolazote = 4-5.

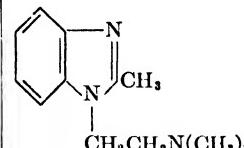
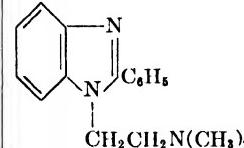
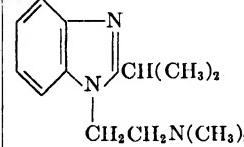
TABLE 53
N-Polymeric derivatives of ethylenediamine
Derivatives of indole

NO.	FORMULA	BOILING POINT °C. 128-129/0.25 mm.	MELTING POINT OF SALT °C. 142 (picrate)	REFERENCES
1...				(460)
2...		102-105/0.2 mm.		(460)
3...		187-189/0.9 mm.	78 (base)	(460)
4...		162-165/0.2 mm.	191 (HCl)	(460)
5...		183-184/3.8 mm.	212 (HCl)	(460)

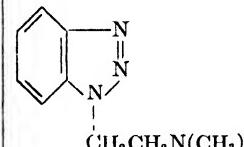
Derivatives of benzimidazole

NO.	FORMULA	BOILING POINT °C. 115-120/0.2 mm.	MELTING POINT OF SALT °C. 235 (2HCl)	REFERENCES
6...				(461)

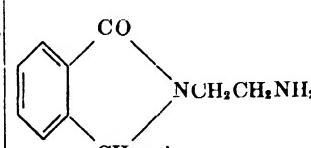
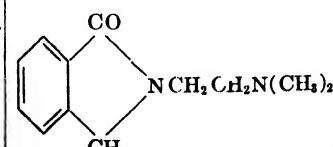
TABLE 53—Continued

NO.	FORMULA	BOILING POINT °C.	MELTING POINT OF SALT °C.	REFERENCES
7...		117/0.3 mm.	239 (2HCl)	(461)
8...			72 (base) 234 d. (2HCl)	(461)
9...		130-136/1.1 mm.	236 (dipicrate)	(461)

Derivatives of benzotriazole

NO.	FORMULA	BOILING POINT °C.	MELTING POINT OF SALT °C.	REFERENCES
10...		115-117/0.3 mm.	171 (HCl)	(461, 462)

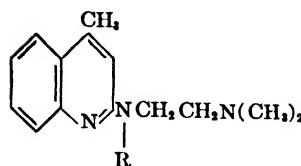
Derivatives of phthalimidine

NO.	FORMULA	BOILING POINT °C.	MELTING POINT OF SALT °C.	REFERENCES
11...			65 (base) 282 (CH3I)	(307)
12...			70 (base) 282 (CH3I) 195 (picrate)	(307)

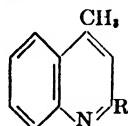
Derivatives of quinoline

NO.	FORMULA	BOILING POINT °C. 175-178/4-5 mm.	MELTING POINT OF SALT °C. 221 (HCl)	REFERENCES
13...				(65)
14...		185-188/7 mm.	194 (picrate) 240 (HCl)	(307)
15...			193 (base·5H2O)	(307)
16...		152-153/10 mm.	195 (HCl)	(307)
17...			216 (HI)	(307)
18...		213-215/5 mm.	225 (HCl) 175 (picrate)	(307)
19...		188/1.6 mm.	136 (citrate)	(244)
20...		155-160/0.2 mm.	247 (HCl)	(244)

TABLE 53—Continued
Derivatives of levodidyl



NO.	R	BOILING POINT °C.	MELTING POINT OF SALT °C.	REFERENCES
21...	C ₆ H ₅ CH ₂ —	158-165/0.06 mm.		(220)
22...	<i>o</i> -ClC ₆ H ₄ CH ₂ —	156/0.03 mm.	215 (HCl)	(220)
23...	<i>p</i> -ClC ₆ H ₄ CH ₂ —	178/0.04 mm.		(220)
24...	2,4-Cl ₂ C ₆ H ₃ CH ₂ —	192/0.05 mm.		(220)
25...	3,4-Cl ₂ C ₆ H ₃ CH ₂ —	183-187/0.03 mm.		(220)
26...		159-172/0.05 mm.		(220)
27...		161-164/0.07 mm.		(220)
28...	<i>p</i> -CH ₃ OC ₆ H ₄ CH ₂ —	180/0.07 mm.		(220)
29...	2,3-(CH ₃ O) ₂ C ₆ H ₃ CH ₂ —	189-191/0.08 mm.		(220)
30...	3,4-(CH ₃ O) ₂ C ₆ H ₃ CH ₂ —	192-193/0.07 mm.		(220)
31...		189-190/0.06 mm.		(220)



NO.	R	BOILING POINT °C.	MELTING POINT OF SALT °C.	REFERENCES
32...		196/0.05 mm.		(220)
33...		176-182/0.05 mm.		(220)
34...			295 d. (2HCl)	(5)

TABLE 53—*Continued*
Derivatives of quinoxaline

NO.	FORMULA	MELTING POINT OF SALT °C.	REFERENCES
			°C. 218 (HCl)
35.....			(156)

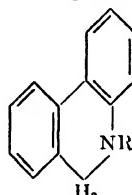
Derivatives of carbazole

NO.	FORMULA	BOILING POINT °C.	MELTING POINT OF SALT OR BASE °C.	REFERENCES
				(HCl)
36....		190–210/4–6 mm.	242 d.	(52, 146)
37....		160/0.9 mm.		(144)
38....			250 (HCl)	(65)
39....			81 (base)	(460)
40....			220 (HCl)	(460)

TABLE 53—Continued

NO.	FORMULA	BOILING POINT °C	MELTING POINT OF SALT OR BASE °C.	REFERENCES
41...		147-149/0.5 mm.	137 (HCl)	(460)

Derivatives of phenanthridine

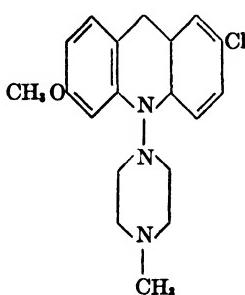


NO.	R	MELTING POINT OF SALT °C.	REFERENCES
42.....	-CH ₂ CH ₂ N(CH ₃) ₂	179 (dimaleate) 184 (dipicrate)	(202)
43.....	--CH ₂ CH ₂ N(C ₂ H ₅) ₂	159 (dipicrate)	(202)
44.....	-CH ₂ CH ₂ N	238 (2HCl) 158 (dimaleate)	(202)
45.....	-CH ₂ CH ₂ N	191 (HCl) 248 (2HCl)	(202)
FORMULA			
46.....		223 (2HCl)	(5)

Derivatives of acridine

NO	FORMULA	MELTING POINT OF SALT	REFERENCES
47.....			(146, 290)

TABLE 53—*Concluded*

NO.	FORMULA	MELTING POINT OF SALT °C.	REFERENCES
48.....		293 (HCl)	(5)

Derivatives of phenoxazine

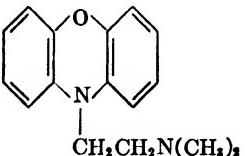
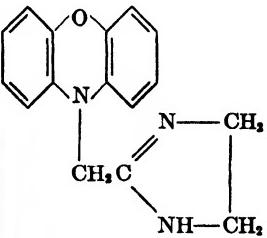
NO.	FORMULA	MELTING POINT OF SALT °C.	REFERENCES
49.....			(146)
50.....		239 (HCl)	(286)

TABLE 54
Correlation of structure and activity in the ethylenediamines (384)



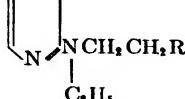
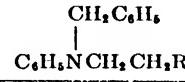
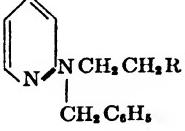
NO.	R	ANTIHISTAMINE ACTIVITY*	
		Intestine†	Asthma‡
1 (F 1571)	—N(C ₂ H ₅) ₂	<1	5
2 (RP 2325)	—N(CH ₃) ₂	6+	20
3.....	—NH ₂		0
			
4.....	—N(CH ₃) ₂	4+	
5.....		1+	
			
6.....	—N(C ₂ H ₅) ₂	13	5
7 (Antergan)	—N(CH ₃) ₂	100	100
8.....	—N(CH ₃) ₂ I ⁺		0
9.....	—N(CH ₃) ₂ ↓ O	2	10-20
10.....		1-2	
11.....		1	
			
12.....	—N(C ₂ H ₅) ₂	1-10	
13(Pyribenzamine)	—N(CH ₃) ₂	200	200
14.....	—N(CH ₃) ₂ I ⁺		
15.....		4-33+	
16.....		0-1+	1+

TABLE 54—Continued



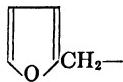
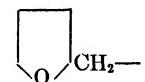
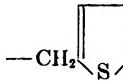
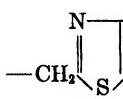
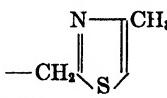
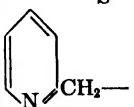
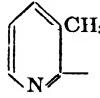
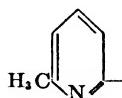
NO.	R	ANTIHISTAMINE ACTIVITY*	
		Intestine†	Asthma‡
17.....	C_2H_5	6	20
18.....	$n\text{-C}_4\text{H}_9$	26	40
19.....	$\text{CH}_2=\text{CHCH}_2-$	6	6
20.....	$\text{HOCH}_2\text{CH}_2-$		<1
21.....	$\text{CH}_3\text{OCH}_2\text{CH}_2-$	140	40
22.....	$\text{C}_2\text{H}_5\text{OCH}_2\text{CH}_2-$	100	50
23.....	$\text{C}_6\text{H}_5\text{CH}_2-$	100	100
24.....	$p\text{-CH}_2\text{OC}_6\text{H}_4\text{CH}_2-$	33	
25.....	$\text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2-$		5
26.....	$\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2\text{CH}_2-$		
27.....	$\text{C}_6\text{H}_5\text{CO}-$		10
28.....	C_6H_5-	50	0-50
29.....		0+	
30.....		100	100
31.....		5	5
32 (Diatrin)		65	65
33.....		65	100
34.....			40
35.....			4

TABLE 54—Continued

NO.	R	ANTIHISTAMINE ACTIVITY*	
		Intestine†	Asthma‡
36.....	C ₂ H ₅	4+	
37.....	<i>i</i> -C ₃ H ₇	2+	
38.....	(CH ₃) ₂ NCH ₂ CH ₂ —	0+	
39 (Pyribenzamine)	C ₆ H ₅ CH ₂ —	200	200
40.....	C ₆ H ₅ CH ₂ CH ₂ —	1+	
41.....	<i>p</i> -CH ₃ C ₆ H ₄ CH ₂ —		100
42.....	<i>p</i> -C ₂ H ₅ C ₆ H ₄ CH ₂ —		10
43 (Neoantergan)	<i>p</i> -CH ₃ OC ₆ H ₄ CH ₂ —	200-250+	1000
44.....	<i>p</i> -C ₂ H ₅ OC ₆ H ₄ CH ₂ —	200	200
45.....	<i>m</i> -CH ₃ OC ₆ H ₄ CH ₂ —		0
46.....	<i>o</i> -CH ₃ OC ₆ H ₄ CH ₂ —	4+	10
47.....	C ₆ H ₅ CO—	0-1+	
48.....	C ₆ H ₅ —	3+	10
49		1-2+	
50 (Foraluminin)		66	200
51 (Histadyl, Thenylene).....		200	200
52 (Bromothen)		400	
53 (Chlorothen)		400	
54			40



NO.	R	ANTIHISTAMINE ACTIVITY	
		Intestine†	Asthma‡
55 (Pyribenzamine)		200	200
56.....		2+	
57.....		4+	
58.....		20+	
59.....		20	
60 (Hetramine)		2-4+	4
61.....		20+	



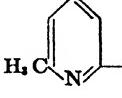
62 (Neoantergan)		200-250+	1000
63.....			20
64.....			10
65.....			2

TABLE 54—Continued

NO.	R	ANTIHISTAMINE ACTIVITY	
		Intestine†	Asthma‡
66 (Neohetramine)		2-4	
67 (White 194B)			10

R = —CH₂CH₂N(CH₃)₂; R' = —CH(CH₃)CH₂CH₂N(CH₃)₂

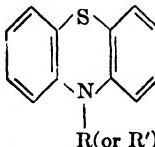
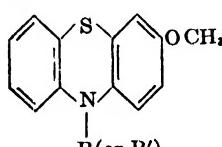
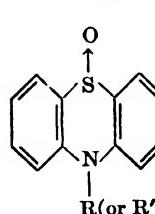
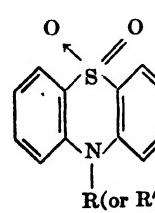
NO.	FORMULA	ANTIHISTAMINE ACTIVITY			
		Intestine		Asthma	
		R	R'	R	R'
68.....		100 (RP 3015)	100 (Phenergan)	100	200
69.....		100	50	100	200
70.....		10			
71.....		50		100	

TABLE 54—*Concluded*

NO.	FORMULA	ANTIHISTAMINE ACTIVITY			
		Intestine		Asthma	
		R	R'	R	R'
72.....	 R(or R')			0	
73.....	 R(or R')			2-4+	

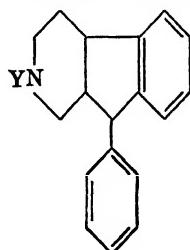
* Antihistaminic activity: Pyribenzamine = 200 (intestine), 200 (asthma).

† Action in relieving spasmolytic action of histamine on isolated guinea-pig intestine.

‡ Action in relieving bronchoconstriction in guinea pigs by histamine aerosol.

TABLE 55
1-Pyridindene derivatives (319, 320)

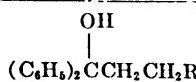
NO.	X	Y	Z	MELTING POINT OF SALT °C.
1.....	H	H	H	204 (HBr)
2.....	H	C ₂ H ₅	H	204 (HBr) 162 (SCN)
3.....	H	<i>i</i> -C ₄ H ₉	H	245 (HBr)
4.....	H	<i>n</i> -C ₆ H ₅	H	195 (HBr)
5.....	7-CH ₃	CH ₃	H	203 (HBr)
6.....	6(or 8)-OCH ₃	CH ₃	H	210 (HBr)
7.....	7-CH ₃	CH ₃	<i>p</i> -CH ₃	203 (HBr)
8.....	6(or 8)-OCH ₃	CH ₃	<i>m</i> -OCH ₃	210 (HBr)
9 (The-phorin) ..	H	CH ₃	H	154 (HCl) 126 (HBr) 171 (maleate) 160 (tartrate) 161 (salicylate) 139 (thiocyanate) 251 d. (methochloride) 114 (methyl <i>p</i> -toluenesulfonate)
10.....	H	C ₂ H ₅	H	162 (thiocyanate)
11.....	H	<i>i</i> -C ₄ H ₉	H	184 (oxalate)
12.....	7-CH ₃	CH ₃	<i>p</i> -CH ₃	186 (oxalate)

TABLE 55—*Concluded*

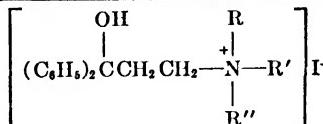
NO.	Y	MELTING POINT OF SALT °C.
13.	CH ₃	261 (HCl) 246 (HBr) 293 (CH ₃ I)
14.	C ₆ H ₅	251 (HBr)

TABLE 56
Aminoalkyl esters, propanols, propenes, propanes, and propanones (I)
 $\text{RNCH}_2\text{CH}_2\text{COOC}_2\text{H}_5$

R	BOILING POINT	MELTING POINT OF SALT	YIELD
	°C.	°C.	per cent
Dibutyl.....			80
Diallyl.....	108-110/15 mm.		80
d-N-Methylamphetamine.....	165-166/12 mm.	126 (acid oxalate)	78
1-Piperidyl.....			85
4-Morpholinyl.....			86
1-Pyrrolidyl.....	108-110/22 mm.		40

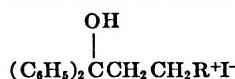


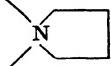
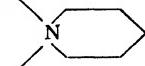
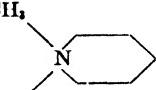
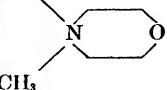
R	BOILING POINT	MELTING POINT	MELTING POINT OF SALT	YIELD
	°C.	°C.	°C.	per cent
Amino.....		143	184 (HCl)	33
Methylamino.....	148-150/0.2 mm.	146	151 (HCl)	24
Ethylamino.....		142	177 (HCl)	38
Benzylamino.....		152	203 (HCl)	16
Dimethylamino.....		166	205 (HCl)	62
Diethylamino.....	154/0.2 mm.	53	203 (HCl)	56
Dipropylamino.....	154/0.1 mm.	53	161 (HCl)	51
Dibutylamino.....	157-159/0.1 mm.	42	109 (HCl)	54
N-Methyl-anilino.....		97	170 d. (HCl)	84
d-N-Methylamphetamine.....		58	208 (HCl)	55
Diallylamo... 1-Pyrrolidyl.....	157-159/0.4 mm.	27	156 (HCl)	60
4-Morpholinyl.....		172	191 (HCl)	63
		106	231 (HCl)	50

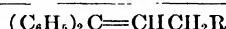


R	R'	R''	MELTING POINT	R	R'	R''	MELTING POINT
			°C.				°C.
CH ₃	CH ₃	CH ₃	243 d.	C ₂ H ₅	C ₂ H ₅	C ₂ H ₅	208
CH ₃	CH ₃	C ₂ H ₅	201 d.	CH ₃	C ₃ H ₇	C ₃ H ₇	183
CH ₃	CH ₃	Phenyl	176 d.	CH ₃	C ₄ H ₉	C ₄ H ₉	196
CH ₃	CH ₃	2-Phenyl-isopropyl	226 d.	CH ₃	Allyl	Allyl	197 d.
CH ₃	C ₂ H ₅	C ₂ H ₅	199	CH ₃	CH ₃	C ₃ H ₇ (bromide)	233
				CH ₃	CH ₃	C ₄ H ₉ (bromide)	235 d.

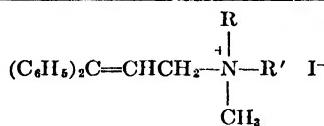
TABLE 56—Continued



R	MELTING POINT °C.	R	MELTING POINT °C.
	210		205
	215		204 d.



R	BOILING POINT °C.	MELTING POINT °C.	MELTING POINT OF SALT °C.
Amino.....	Decomposes at 0.1 mm.		215 d. (HCl)
Ethylamino.....	116-117/0.15 mm.		179 d. (HCl)
Dimethylamino.....	192-193/18 mm.		170 (HCl)
Diethylamino.....	111/0.05 mm.		147 (HCl)
Dipropylamino.....	146-148/0.4 mm.		129 (HCl)
Dibutylamino.....	139-142/0.05 mm.		150 (HCl)
N-Methylanilino.....	200-204/0.5 mm.		
d-N-Methylamphetamine.....	168-170/0.07 mm.		164 (acid ox- alate)
Diallylamino.....	134/0.2 mm.		
1-Pyrrolidyl.....	125/0.02 mm.		167 (HCl)
1-Piperidyl.....	138/0.1 mm.		210 (HCl)
4-Morpholinyl.....		72	219 (HCl)



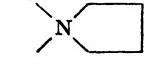
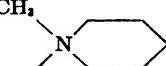
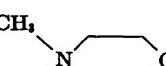
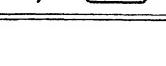
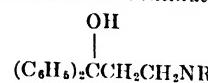
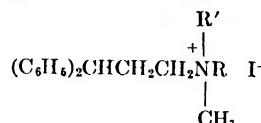
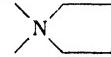
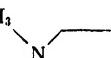
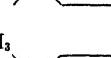
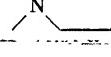
R	R'	MELTING POINT °C.	R, R'	MELTING POINT °C.
CH ₃	CH ₃	205 d.		154
C ₂ H ₅	C ₂ H ₅	186		
C ₃ H ₇	C ₃ H ₇	158 d.		
C ₄ H ₉	C ₄ H ₉	125		
CH ₃	—CH(CH ₃)CH ₂ C ₆ H ₅	151 d.		190 d.
Allyl	Allyl	151 d.		164

TABLE 56—Continued



R	BOILING POINT °C.	MELTING POINT °C.	MELTING POINT OF SALT °C.
Ethyl.....			164 (HCl)
Dimethyl.....	183–185/16 mm.	45	170 (HCl)
Dipropyl.....			115 (HCl)
Dibutyl.....			114 (HCl)
1-Pyrrolidyl.....	125/0.02 mm.		136 (HCl)
1-Piperidyl.....		41	217 (HCl)
4-Morpholinyl.....			209 (HCl)



R	R'	MELTING POINT °C.	R, R'	MELTING POINT °C.
CH ₃	CH ₃	180	CH ₃ 	157
C ₂ H ₅	C ₂ H ₅	163	CH ₃ 	
C ₃ H ₇	C ₃ H ₇	145	CH ₃ 	176 d.
C ₄ H ₉	C ₄ H ₉	143	CH ₃ 	163



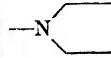
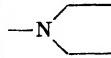
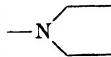
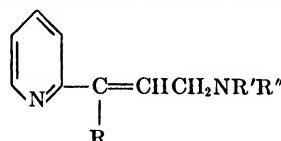
R	NR'R''	MELTING POINT OF SALT OR BASE °C.
C ₆ H ₅ —	—N(CH ₃) ₂	153 (HCl)
C ₆ H ₅ —	—N(C ₂ H ₅) ₂	112 (HCl)
C ₆ H ₅ —	—N 	164 (HCl)
C ₆ H ₅ —	—N 	190 (HCl)
C ₆ H ₅ —	—N 	182 (HCl)

TABLE 57—Concluded

R	NR'R"	MELTING POINT OF SALT OR BASE °C.
p-ClC ₆ H ₄ —	—N(—C ₆ H ₄) ₂	98 (base) 152 d. (oxalate)
p-ClC ₆ H ₄ —	—N(—C ₆ H ₄ O)C ₆ H ₄	84 (base) 165 d. (oxalate)
p-CH ₃ OC ₆ H ₄ —	—N(CH ₃) ₂	90 (base) 209 d. (2HCl)
	—N(CH ₃) ₂	67 (base)



R	NR'R"	BOILING POINT	MELTING POINT OF SALT °C.
C ₆ H ₅ —	—N(CH ₃) ₂	108/0.05 mm.	182 (HCl)
C ₆ H ₅ —	—N(C ₂ H ₅) ₂	119–121/0.01 mm.	155 d. (oxalate)
C ₆ H ₅ —	—N(—C ₆ H ₄) ₂	128–135/0.01 mm.	167 d. (oxalate) 153 d. (mucate)
C ₆ H ₅ —	—N(—C ₆ H ₄ O)C ₆ H ₄	154–158/0.01 mm.	170 d. (oxalate)
p-ClC ₆ H ₄ —	—N(CH ₃) ₂	118–120/0.01 mm.	171 d. (oxalate) 166 d. (maleate)
p-ClC ₆ H ₄ —	—N(C ₂ H ₅) ₂	136–138/0.01 mm.	152 d. (oxalate)
p-ClC ₆ H ₄ —	—N(—C ₆ H ₄) ₂	165–169/0.01 mm.	177 d. (oxalate) 149 d. (maleate)
p-ClC ₆ H ₄ —	—N(—C ₆ H ₄ O)C ₆ H ₄	182–184/0.01 mm.	168 d. (oxalate)
p-ClC ₆ H ₄ —	—N(—C ₆ H ₄ O)C ₆ H ₄	186–188/0.01 mm.	181 d. (oxalate)
p-CH ₃ OC ₆ H ₄ —	—N(CH ₃) ₂	156–158/0.3 mm.	208 d. (2HCl)
	—N(CH ₃) ₂	116–122/0.5 mm.	162 d. (oxalate)

TABLE 58
Bridged-ring propylamines (95, 146)

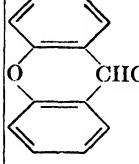
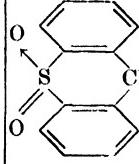
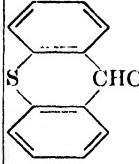
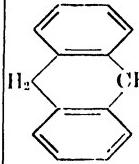
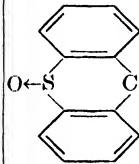
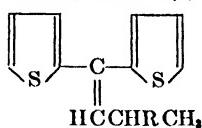
NO.	FORMULA	NO.	FORMULA
1		4	
2		5	
3		6	$(C_6H_5)_2CHCH_2CH_2N(CH_3)_2$
		7 (Aspasan) (28)	$(C_6H_5)_2CHCH_2CH_2N(CH_3)_2$

TABLE 59
Amidines and imidazolines of aminoalkanes

NO.	FORMULA	MELTING POINT OF SALT OR BASE °C.	REFERENCES
1.....	$\begin{array}{c} (\text{C}_6\text{H}_5)_2\text{CHCH}_2\text{C} \equiv \text{N}-\text{CH}_2 \\ \\ \text{NH}-\text{CH}_2 \end{array}$	101 (base) 90 ($\text{HCl}\cdot\text{H}_2\text{O}$) 170 (picrate)	(212)
2.....	$\begin{array}{c} (\text{C}_6\text{H}_5)_2\text{CHCH}_2\text{C} \equiv \text{NH} \\ \\ \text{NH}_2 \end{array}$	209 (picrate)	(212)
3.....	$\begin{array}{c} (\text{C}_6\text{H}_5)_2\text{CHCH}_2\text{C} \equiv \text{NH} \\ \\ \text{N}(\text{CH}_3)_2 \end{array}$	249 (HCl)	(212)
4.....	$\begin{array}{c} (\text{C}_6\text{H}_5)_2\text{CHCH}_2\text{C} \equiv \text{NH} \\ \\ \text{N} \\ \text{C}_6\text{H}_5 \end{array}$	250 (HCl)	(212)
5.....	$\begin{array}{c} (\text{C}_6\text{H}_5)_2\text{CHC} \equiv \text{NH} \\ \\ \text{NH}_2 \end{array}$	225 (picrate)	(212)
6.....	$\begin{array}{c} (\text{C}_6\text{H}_5)_2\text{CHC} \equiv \text{N}-\text{CH}_2 \\ \\ \text{NH}-\text{CH}_2 \end{array}$	135 (base) 182 (HCl) 185 (picrate)	(12, 212)
7.....	$\begin{array}{c} \text{C}_6\text{H}_5\text{CH}_2\text{C} \equiv \text{N}-\text{CH}_2 \\ \\ \text{NH}-\text{CH}_2 \end{array}$	62 (base) 172 (HCl)	(283)
8.....	$\begin{array}{c} \text{C}_6\text{H}_5\text{CH}_2\text{C} \equiv \text{N}-\text{CH}_2 \\ \\ \text{NH}-\text{CH}_2 \end{array}$	120 (base) 253 (HCl)	(283, 397)
9.....	$\begin{array}{c} p\text{-C}_6\text{H}_4\text{C}_6\text{H}_4\text{CH}_2\text{C} \equiv \text{N}-\text{CH}_2 \\ \\ \text{NH}-\text{CH}_2 \end{array}$		(70)

TABLE 60
Dithienylbutenes (3)



NO.	R	MELTING POINT OF HYDROCHLORIDE °C.
1.....	—NHCH ₃	170
2.....	—NHC ₂ H ₅	153
3.....	—N Cyclohexyl	169
4.....	—N Cyclohexyl	189
5.....	—N Cyclohexyl O	182

TABLE 61
Amino esters of substituted alicyclic carboxylic acids (424, 440)
 2-Diethylaminoethyl esters

NO.	CARBOXYLIC ACID	MELTING POINT OF HYDROCHLORIDE	ANTIHISTAMINE ACTIVITY*
		°C.	
1	1- α -Naphthylcyclohexane	185	20
2	1-Benzylcyclohexane	150	1
3	2-Methyl-1-phenylcyclohexane	128	5
4	1-Phenylcyclohexane	161	10
5	1-Cyclohexylcyclohexane	166	5
6	2-Phenylcyclohexane	76	
7	2-Cyclohexylcyclohexane	109	0.5
8	2-Benzoyl- Δ^4 -cyclohexene	133	5
9	2-Benzoylcyclohexane	100	20
10	2-Hexahydrobenzoyl- Δ^4 -cyclohexene (diastereoisomers)	122	
11	2-Hexahydrobenzoylcyclohexane (diastereoisomers)	136	5
12	2-Benzylcyclohexane	116	5
13	4-Phenylcyclohexane	162	5
14	4-Cyclohexylcyclohexane	192	10
15	1- α -Naphthylcyclopentane	176	5
16	2-Phenyl-2-indane	162	5
17	1-Benzylcyclopentane	122	1
18	2-Methyl-1-phenylcyclopentane	145	5
19	1-Phenylcyclopentane	144	5
20	2-Methyl-1-cyclohexylcyclopentane	143	1
21	1-Cyclohexylcyclopentane	128	5
22	3-Methyl-1-phenylcyclobutane	139	5
23	1-Phenylcyclobutane	146	
24	1-Cyclohexylcyclobutane	127	10
25	2-Methyl-2-phenylcyclopropane	81	10
26	1-Phenylcyclopropane		

2-Dimethylaminoethyl esters

27	1-Phenylcyclohexane	177	5
28	2-Cyclohexylcyclohexane	142	1
29	2-Methyl-1-phenylcyclopentane	138	5
30	1-Phenylcyclopentane	118	5

1-Phenylcyclohexanecarboxylates

NO.	AMINO ALCOHOL	MELTING POINT OF HYDROCHLORIDE	ANTIHISTAMINE ACTIVITY*
		°C.	
31	2-Dimethylaminoethoxyethyl	130	10
32	3-Piperidino-2-hydroxypropyl	145	10
33	3-Piperidino-2-phenylurethanpropyl	164	50
34	1,3-Bis(diethylamino)-2-propyl	137	5
35	1,2-Divinylene-1,4,5,6-tetrahydro-5-pyrimidyl	188	5
36	2,2-Bis(hydroxymethyl)-2-aminoethyl	214	5

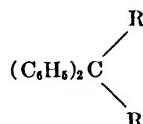
* Minimum dose of test compound necessary to antagonize 0.1 γ /ml. of histamine diphosphate on isolated guinea-pig intestine. Benadryl = 0.02.

TABLE 62
2-Diethylaminoethyl benzilate hydrochlorides (30)
 $R(R'C_6H_4)C(OH)COOC_6H_5CH_2N(C_2H_5)_2 \cdot HCl$

NO.	R	R'	MELTING POINT	ANTIHISTAMINE ACTIVITY*
			°C.	
1.....	H	H		1
2.....	4-CH ₃ OC ₆ H ₄ —	H	171	0.2
3.....	4-C ₂ H ₅ OC ₆ H ₄ —	H	174	0.1
4.....	4-n-C ₃ H ₇ OC ₆ H ₄ —	H	142	0.5
5.....	4-i-C ₃ H ₇ OC ₆ H ₄ —	H	162	0.33
6.....	4-n-C ₄ H ₉ OC ₆ H ₄ —	H	148	1
7.....	4-i-C ₄ H ₉ OC ₆ H ₄ —	H	142	0.5
8.....	4-n-C ₆ H ₁₁ OC ₆ H ₄ —	H	137	1
9.....	4-i-C ₆ H ₁₁ OC ₆ H ₄ —	H	135	0.5
10.....	4-n-C ₆ H ₁₃ OC ₆ H ₄ —	H	125	1
11.....	4-n-C ₇ H ₁₅ OC ₆ H ₄ —	H	132	
12.....	4-n-C ₈ H ₁₇ OC ₆ H ₄ —	H	127	
13.....	4-n-C ₁₀ H ₂₁ OC ₆ H ₄ —	H	125	
14.....	4-C ₆ H ₅ OC ₆ H ₄ —	H	154	0.5
15.....	4-C ₆ H ₅ CH ₂ OC ₆ H ₄ —	H	149	0.25
16.....	2,5-(C ₂ H ₅ O) ₂ C ₆ H ₃ —	H	153	
17.....	3,4-(C ₂ H ₅ O) ₂ C ₆ H ₃ —	H	140	
18.....	4-n-C ₄ H ₉ OCH ₂ CH ₂ OC ₆ H ₄ —	H	117	
19.....	4-C ₆ H ₅ OCH ₂ CH ₂ OC ₆ H ₄ —	H	130	1
20.....	4-n-C ₄ H ₉ OC ₆ H ₄ —	4-n-C ₄ H ₉ O—	123	

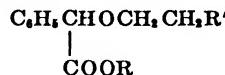
* Activity on isolated guinea-pig gut stimulated by histamine.

TABLE 63
Benzhydryl esters and ketones



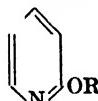
NO.	R	R'	BOILING POINT	MELTING POINT OF HYDRO-CHLORIDE	REFERENCES
			°C.	°C.	
1...	H	—COOCH ₂ CH ₂ N(CH ₃) ₂		163	(6)
2...	H	—COCH ₂ N(CH ₃) ₂	155-175/2 mm.	179 d.	(6)
3...	H	—COCH ₂ CH ₂ N(CH ₃) ₂	161-162/1.5 mm.	160	(6)
4...	—OCH ₂ CH ₂ N(CH ₃) ₂	—COOCH ₂ CH ₂ N(CH ₃) ₂	188-190/0.7 mm.		(294, 295)
5...	—OCH ₂ CH ₂ N(CH ₃) ₂	—COOCH ₂ N 			(294)

TABLE 64
Alkyl 1-(α -dialkylaminoalkoxy)phenylacetates (429)



NO.	R	R'	BOILING POINT	MELTING POINT OF HYDRO-BROMIDE
1.....	CH ₃	—N(CH ₃) ₂		
2.....	CH ₃	—N(C ₂ H ₅) ₂	160–165/4 mm.	201
3.....	CH ₃	—N 	168–170/4 mm.	
4.....	C ₂ H ₅	—N(CH ₃) ₂	145–146/3 mm.	
5.....	C ₂ H ₅	—N(C ₂ H ₅) ₂	148–150/2 mm.	
6.....	C ₂ H ₅	—N 	178–182/2 mm.	
7.....	C ₂ H ₅	—N 	177–179/3 mm.	
8.....	i-C ₃ H ₇	—N(CH ₃) ₂	129–133/2 mm.	
9.....	i-C ₃ H ₇	—N(C ₂ H ₅) ₂	150–155/3 mm.	
10.....	i-C ₃ H ₇	—N 	140–144/4 mm.	
11.....	i-C ₃ H ₇	—CH ₂ N(CH ₃) ₂	138–140/2 mm.	
12.....	i-C ₃ H ₇	—N(C ₄ H ₉) ₂	170–173/4 mm.	
13.....	n-C ₆ H ₁₃	—N(CH ₃) ₂	140–144/4 mm.	
14.....	n-C ₆ H ₁₃	—N(n-C ₄ H ₉) ₂	130–135/4 mm.	
15.....	n-C ₆ H ₁₃	—N 	155–159/3 mm.	
16.....	n-C ₆ H ₁₃	—N(C ₃ H ₇) ₂	160–163/1 mm.	
17.....	n-C ₆ H ₁₃	—CH ₂ N(C ₂ H ₅) ₂	190–193/7 mm.	
18.....	C ₆ H ₅ CH ₂ —	—N(CH ₃) ₂		213
19.....	C ₆ H ₅ CH ₂ —	—N 		230
20.....	C ₆ H ₅ CH ₂ —	—N(C ₂ H ₅) ₂	195–199/3 mm.	
21.....	C ₆ H ₅ CH ₂ —	—N(n-C ₄ H ₉) ₂	200–205/3 mm.	

TABLE 65
2-Pyridyl amino esters (190)



NO.	R	BOILING POINT °C.	MELTING POINT OF SALT °C.
1	COOCH ₂ CH ₂ N(C ₂ H ₅) ₂	170-171/1 mm.	
2	COOCH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂	179-180/1 mm.	
3	COOCH ₂ CH ₂ N(C ₂ H ₅) ₂	169-170/1 mm.	112 (2HCl)
4	COOCH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂	174-175/1 mm.	130 (2HCl)
5	COOCH ₂ CH ₂ N(C ₂ H ₅) ₂	184-185/1 mm.	142 (2HCl)
6	COOCH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂	187-189/1 mm.	164 (2HCl)
7	COOCH ₂ CH ₂ N(C ₂ H ₅) ₂		140 (2HCl)

TABLE 65—*Concluded*

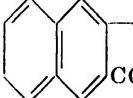
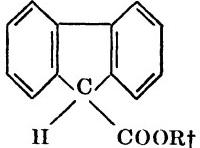
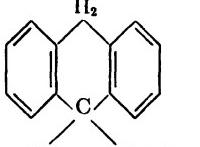
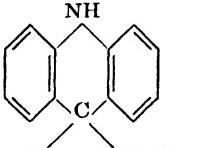
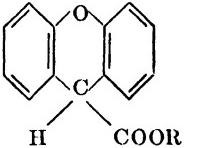
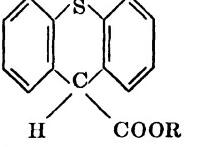
NO.	R	BOILING POINT	MELTING POINT OF SALT
8			°C. 151 (2HCl)
9	—CH ₂ COOCH ₂ CH ₂ N(C ₂ H ₅) ₂	103-105/0.14 mm.	96 (HCl)
10	—CH ₂ COOCH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂	114-115/0.2 mm.	
11	—CHCOOCH ₂ CH ₂ N(C ₂ H ₅) ₂ CH ₃	121-123/1 mm.	
12	—CHICOOC ₂ H ₅ CH ₂ CH ₂ N(C ₂ H ₅) ₂ CH ₃	122-123/0.4 mm.	
13	—CHCOOCH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂ C ₆ H ₅		112 (2HCl)
14	—CHCOOCH ₂ CH ₂ CH ₂ N(C ₂ H ₅) ₂ C ₆ H ₅		

TABLE 66
Bridged esters (239, 240)

NO.	FORMULA	ANTIHISTAMINE ACTIVITY*
1.....		1
2.....		0.05
3.....		2
4.....		0.4
5.....		0.33

* Antihistamine ratio (papaverine = 1.5). Action on isolated intestine of guinea pig against spasm caused by $2 \times 10^{-6} M$ histamine acid phosphate.

† R is 2-diethylaminoethyl.

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